THE HUMAN APOCRINE SWEAT GLAND IN HEALTH AND DISEASE

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A Monograph in

AMERICAN LECTURES IN DERMATOLOGY

Edited by

ARTHUR C. CURTIS, M.D.

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Ann Arbor, Michigan

The HUMAN APOCRINE SWEAT GLAND in HEALTH and DISEASE

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DEDICATED

to

Jeanne and Marguerite

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H J H
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THE HUMAN APOCRINE SWEAT GLAND IN HEALTH AND DISEASE



Frontispiece. Apopilosebaceous unit. A small piece of freshly excised axillary skin was stained with methylene blue (0.1%) and gentle dissection employed to expose the above structures. The stratum corneum at the top of the photograph has been partially reflected back. An almost straight black hair extends down from the skin to the center of the photograph. The coiled mass of tubules (right lower) is an apocrine sweat gland. At its upper pole one can see the apparent beginning of the apocrine duct. Note that it uncoils, then proceeds upward parallel with the hair over the lobulated blue-staining sebaceous glands to open at the upper end of the hair follicle. At this upper end of the hair follicle also a second apocrine duct with prominent dilated funnel-shaped opening can be seen to open into this same follicle on the opposite side. This duct was severed from its glandular component during the dissection.

I

INTRODUCTION

Within recent years, there has been a rapidly increasing store of information concerning the physiology and pathology of the cutaneous appendages of man However, one of these appendages, viz, the apocrine sweat gland, has received considerably less attention than have the others While the eccrine sweat glands are found over almost the entire skin surface, the apocrine sweat glands are limited to certain well-defined areas, such as the axilla, anogenital region, the mammary areola, the ear canal (ceruminous glands) and the eyelid (glands of Moll) The restriction of the apocrine glands to such sites parallels the regression of terminal body hair and is believed to represent an evolutionary change In lower forms, such as the horse and dog apocrine glands associated with body hair are found over almost the entire cutaneous surface Because of the special localization of the apocrine glands in man, plus the fact that they have been regarded as atavistic organs little effort was made to examine them in greater detail

One of the first descriptions of the "large sweat glands" of the axilla was made by Professor Horner of the Department of Anatomy, of the University of Pennsylvania, in 1846 (1) Later descriptions by Krause (3) and by Robin (2), who described these glands in the inguinal region and pointed out that they were visible grossly, were noteworthy Heynold (4) described the apocrine glands of the ear canal in detail, in 1876 The first mention of the nature of apocrine sweat was made in 1852 by von Kolliker (5) He described it as "whitish-yellow, tolerably-viscid" matter a rather accurate description in light of our present knowledge One is unable to find any additional information of

significance regarding the secretion of the apocrine sweat glands up to the present day

Other isolated reports on the apocrine sweat gland appeared prior to and after the turn of the century However, it was not until 1922 that Schiefferdecker wrote the first really extensive account of the human apocrine sweat glands (6) This author detailed the anatomy of the apocrine sweat glands, emphasized the racial variations seen, and formulated an anthropological hierarchy based on the number and location of these glands He proposed that the fewer the number of apocrine sweat glands present, the higher the developmental state He found the highest level of development to be represented by the Nordic male, while the Australasian and Negro, with larger and more numerous glands, and with apocrine glands less restricted in localization were at the bottom of the scale Other races fell in between In general females, with greater numbers of apocrine sweat glands were thought less evolved than males

One of the primary points of interest regarding the apocrine sweat glands during this period concerned the development of these glands at puberty, and the influence of endocrine states and age on their function Much of this work was controversial and will be discussed later in this report

Another interesting facet of the development of the apocrine sweat glands concerned the claim that apocrine glands may undergo metamorphosis into eccrine sweat glands during adult life (von Eggeling) (7) We are promptly reminded of the claims of Kuno (8) and O'Brien (9) that there may be intermediate sweat glands which possess properties of each, and defy strict histologic classification

For all practical purposes, the physiology and pharmacology of the apocrine sweat glands have been completely ignored through the years *The innervation, means of stimulation, mechanisms involved in apocrine function, and the pharmacology* were unknown and little mention of these features can be found in the literature The study of Olivet and Nauck in 1930 on apocrine sweat gland *function was one of the few that was available* (10) These authors, studying the histology of biopsy specimens of axillary skin previously stimulated by various drugs, reached the

rather unlikely conclusion that atropine stimulated and epinephrine inhibited the apocrine sweat glands Except for the time honored notion that these were "scent glands" similar to those in the lower mammalia, no other concept of their importance to man was available

The pathologist, however, perhaps stimulated by the dermatologist who noted peculiar eruptions limited to apocrine areas, incriminated the apocrine sweat gland in several dermatoses Fox-Fordyce disease (1902) and hidradenitis suppurativa (1933) became known as "apocrine" disorders However, as is often the case where basic knowledge of the morphology and function of a structure is lacking, the pathogenesis of these diseases was not understood

Our investigative program on the apocrine sweat gland began in May, 1951 It continued through 1956 comprising therefore some five years of study During this period there was a renewed interest in the cutaneous appendages by some anatomists and histochemists, notably Montagna and this served as a great impetus In addition, Yas Kuno, the renowned Japanese physiologist who has contributed so much to our knowledge of eccrine sweat gland function, stimulated us by the excellence of his work

The bulk of the observations made in these studies concerns the apocrine sweat glands of the axilla The axillary apocrine sweat glands are the largest, best developed and most numerous in human skin no matter what the race of the subject studied Furthermore it is relatively easy to utilize the axilla experimentally While some criticism as to extrapolation of our findings to apocrine sweat glands of other regions can be made we feel that for the most part, such extension of our observations may be made with confidence Correlative studies of the apocrine glands of the human ear canal have verified this assumption (11)

Apocrine gland tumors have not been included in this book since we have not had an opportunity to study these lesions experimentally

II

THE ANATOMY OF THE APOCRINE SWEAT GLAND

A. METHODS AND MATERIALS

This work is based on observations made on over two hundred biopsy specimens. The great majority of these were taken from the axillae of normal adult male volunteers between the ages of 19 and 75 years of age. Several specimens were also obtained from male and female bodies at autopsy. In addition to the axilla, from which most of our material was secured, samples from the inguinal region, chest, abdomen, face, and scalp were also included.

Examination of gross morphology was accomplished in some cases by *in vivo* study of the axillary structures after incision of the skin and reflection of the skin edges with Allis forceps. In addition, micro-dissection of axillary skin specimens after staining with 0.1% methylene blue was employed, along with special techniques for the preparation of whole mounts. These methods are described further in the captions beneath the photographs.

Staining techniques used included routine hematoxylin and eosin, phosphotungstic acid-hematoxylin, periodic acid-Schiff stains with and without diastase (12), Gomori's Prussian blue stain for iron (13), silver stain of Perez (14) and the cholinesterase technique (Koelle) (15). Appropriate fixatives were employed throughout. In addition, unstained specimens were studied after frozen sectioning (10-20 microns) and sectioning of paraffin-imbedded tissue (6-10 microns). It should be emphasized that all of the biopsies taken were of adequate size and depth. Relatively large biopsies are necessary in order to insure visualization of entire apocrine sweat glands as well as adjacent glands and related structures.

B EMBRYOLOGY

The apocrine sweat gland is a derivative of the primary epithelial germ as are the sebaceous gland and hair follicle (16) Actually, at an early stage of development, about the fourth to fifth intrauterine month, all hair follicles over most of the skin surface, have the potential to develop apocrine sweat glands At this time, a small nipple-like downgrowth appears at the upper end of the hair follicles This downgrowth consists of a solid cord of epithelial cells It continues to extend and develop into apocrine gland rests in only a small percentage of hairs, however, primarily in those of the axilla, ano-genital region, mammary areola and ear canal but also irregularly on parts of the trunk, scalp and face In the rest of the skin, the apocrine bud gradually diminishes in size and is eventually lost as a part of the hair follicle or adjacent epidermis It should be noted that the point at which the downgrowth appears is about at the junction of the hair follicle and epidermis This is an anatomical relationship that is retained even at full development for the apocrine duct of the adult apocrine gland opens at a high level far up near the hair follicle orifice While the hair follicle should be regarded as the site of origin of the apocrine bud the close proximity of the bud to the epidermis readily explains the occasional extra-follicular apocrine duct one sees in the adult It would appear that the apocrine bud migrates or pulls away from the follicle to develop independently

Extension of the apocrine downgrowth is continued with coiling and cleft formation in the center of the coiled cords Eventually, a lumen is formed and subsequent differentiation into glandular and ductal portions occurs by the seventh to eighth months At birth however and for several years thereafter, the apocrine glands while distinguishable histologically are non-functional and are mere rests in essentially all apocrine areas except the ear canal In this site full development of the apocrine glands occurs before birth Thus these apocrine glands, which are called ceruminous glands in sharp contrast with other apocrine glands of the skin, are fully functioning at birth and are apparently under a different endocrine control In the apocrine sweat glands, myoepithelial cells are not present at birth but differentiate some time thereafter

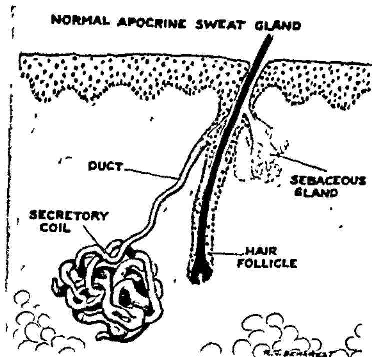


Fig 1 Drawing of apocrine sweat gland Observe shunts and diverticuli along course of tubules in secretory portion of the gland Duct opening into hair follicle ordinarily enters at a higher point than shown in this drawing

The secretory cells of the apocrine sweat gland are devoid of granules at birth with comparatively low cytoplasm indicating the lack of secretory activity (17)

The puberal era marks the period during which full activation of the apocrine sweat glands occurs Paralleling the change in the apocrine glands is the growth of the terminal hair in the same regions Significantly the mammary gland, an apocrine gland anatomically also does not reach full development until puberty

C MORPHOLOGY

The apocrine sweat gland can be classified anatomically as a simple tubular gland *with shunts and diverticuli* It is *simple* since it has a single duct which proceeds from the coiled glandular mass below and empties above into the hair follicle It is a *tubular*

gland in contrast to an alveolar or tubulo-alveolar gland since its secretory component consists essentially of a coiled tube. However, *careful examination (Fig. 1) of the gland reveals that some* parts of the tube are bridged by small shunts, while in other areas, pouch-like projections or diverticuli are present. It should be recalled that these variations of the simple tube as seen in the apocrine gland are not a feature of the eccrine sweat gland coil.

The apocrine sweat gland is grossly visible without the aid of magnification or special staining. If one incises and then reflects the skin of an apocrine gland-bearing area, visualization of the *apocrine sweat glands as small yellow or reddish-yellow globular* masses approximately 1 mm diameter in the deep dermis and subcutaneous tissue is readily made (Figs. 2 and 3). The reddish tint of the glands which has been attributed to increased amounts of iron, is quite variable in its appearance. The relatively great size of the apocrine sweat gland should be easily appreciated for the eccrine sweat gland (approximately ten times smaller) and sebaceous gland are visible only after some degree of magnification.

On casual examination, apocrine glands may appear to be broken into lobules. Close inspection, however, reveals that this is not the case, and the apparent lobules are really all part of the same gland.

Negroes have apocrine sweat glands of relatively great size. They are larger than those of the White race (Fig. 2).

In general, the apocrine duct is much shorter in proportion to the gland than is the eccrine duct to the eccrine gland, (see frontispiece). However, this is not always true for occasionally the apocrine duct shows a loop or coil along its course, indicating longer length in these instances. The point of demarcation of the apocrine duct from the tubule can be precisely marked only under histologic examination, although some change in calibre of the ductal diameter can be seen grossly (see *Frontispiece*). As in the eccrine gland, the initial portion of the apocrine duct usually begins within the coiled mass but is generally coiled for a shorter distance in the apocrine than in the eccrine gland. At its upper end, the apocrine duct becomes funnel-shaped (infundibulum) as the duct opens (above the sebaceous ducts) into the upper end of the hair follicle (Fig. 4), or separately onto the skin



Fig 7 White and Negro apocrine sweat glands The axillary skin was incised and reflected with Allis forceps Adult White man's skin (above) and adult Negro man's skin (below) Globular bodies beneath skin surface are apocrine sweat glands. Although magnification for each photograph was slightly different glands of the Negro are larger Mag × 3½ (upper) × 4 (lower)

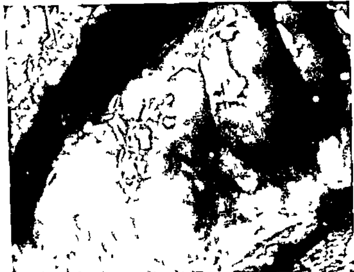




Fig. 3 Negro apocrine sweat gland. Same as Negro skin of Fig. 2 but under higher magnification (x 8). Note some of the vessels supplying these glands.

Fig. 4 Apocrine duct opening into hair follicle. Histological view of apocrine duct as it enters hair follicle. Note dilatation of the duct shown here. This resulted from experimentally produced ductal occlusion (cf. Apocrine Sweat Retention) and is abnormal. Compare with normal duct of Figure 5. H. and E. Mag. x 100

surface Quite commonly, more than one apocrine duct empties into the same hair follicle (frontispiece) On occasion, even three ducts have been observed opening into the same follicle

D TOPOGRAPHICAL RELATIONSHIP — LOCATION IN SKIN

Fundamentally, apocrine sweat glands are oriented anatomically in relation to hair, more specifically, the terminal body hair of the area in which they are found Thus they are part of an "apo-pilo-sebaceous unit" As mentioned previously, it is true that a few apocrine ducts are extra-follicular *in location*, but *all* are derived embryologically from the primary epithelial germ and much of their development and functional activity parallels that of the hair of these areas The main body of the apocrine gland lies deep in the true skin in the deeper portions of the corium and upper subcutaneous tissue They appear densely packed together in most areas such as the axilla (Fig 2), although there are probably only a few thousand glands per axilla as compared with four *to five times as many eccrine sweat glands in the same area* The axilla contains the greatest number of apocrine sweat glands and it is our finding that the overall size of the individual gland is larger there than elsewhere

In contrast to the eccrine sweat glands which are found over almost the entire skin surface, the apocrine sweat glands are restricted to a few well defined areas such as the axilla, the inguinal region perianal skin the mammary areola and less consistently on parts of the trunk *such as the umbilicus and hairy region of* the chest In addition there are apocrine glands in the ear canal (ceruminous glands) and in the eyelid (glands of Moll) Finally the mammary gland, a cutaneous derivative is an apocrine gland

Apocrine sweat glands in areas other than the above are considered heterotopic in location (18) However we have been impressed with the numbers of apocrine glands found on the face especially the malar region of the cheeks These facial glands are considerably smaller than were *those of the axilla but are typical* structurally Similarly the scalp shows apocrine elements not uncommonly (18) It is our feeling that deeper cuts and more thorough examination (utilizing serial sections) of routine biopsies from these areas would disclose the presence of these glands with

much greater frequency than has been perceived heretofore The quantities of sweat secreted from these glands is quite small and consistent with the size of the glands Moreover, it is probable that many of these glands are non-functional

E HISTOLOGY AND HISTOCHEMISTRY

The histologic appearance of all apocrine glands is distinctive The very designation "apocrine" resulted from an interpretation of the method of secretion of these glands based on the histology *Apo*—is a Greek root meaning "from" and apocrine secretory cells appear to be losing the apical tip of the cell histologically, a decapitation (Fig 7) Thus, part of the cell appears to be lost in the apocrine secretion In contrast, eccrine glands form a fluid product without appreciable loss of any of the secretory cell This is referred to as merocrine secretion

Histologic visualization of eccrine sweat glands reveals none of the pinched-off luminal tips of the tubular cells, as seen in the apocrine glands It is interesting in this respect that Kuno has described eccrine secretory cells which do show such changes in Japanese (8) Also, O'Brien has referred to an "intermediate" gland in some biopsies he has studied which have both apocrine and eccrine characteristics (9) The significance of such variations is not entirely clear but may reflect racial differences Finally, the third glandular type, the holocrine gland, is also represented by a cutaneous appendage the sebaceous gland In this type of secretion all of the cell is lost in the secretory process This is a much steadier and slower phenomenon than eccrine or apocrine secretion

The ductal portion of the apocrine sweat gland is difficult if not impossible to distinguish from that of the eccrine gland on histologic appearance alone Both have a double layer of basophilic staining cuboidal cells devoid of myoepithelium, but with a well-defined basement membrane (Fig 5) The apocrine duct is believed to be of slightly larger caliber and some authors feel the cells show more eosinophilia than does the eccrine duct, but it is our feeling that such variations are insignificant and not of value in differentiation The transition from tubule to duct is quite abrupt in the apocrine sweat gland The intraepidermal



Fig 5 Apocrine duct Normal apocrin duct hist l gi ally sit cent rsh n f the l Several cuts of the du t are seen Observe chara teristic d ubl l ver of cuboidal cells H an l L Mag x 240

Fig 6 Apocrine e retory tubule Cross secti n f aj ocrine secret ry tubul sh w ing single layer of c lumnar se ret ry cells Bas ment m mbr n and my epithelial cells are evi lent C mpare with Figur s 10 and 21 in stu ly of my epithelium PAS positive materi l (not glyc en) is pres nt in cyt pl ism f secretory cells After diastase incubati n this disappears PAS stain (bef r diastase) with Harris hem itoxylin count rstain Mag x 510

end of the apocrine duct is marked by the presence of a luminal hyaline fringe, the cuticle, which is similarly visualized at this level in the eccrine duct. Unlike the eccrine duct, the intra-epidermal portion of the apocrine duct is straight and not coiled in appearance. There is some keratinization near the open end of the apocrine duct, also as in the eccrine duct. Histochemically, the apocrine duct shows cytoplasmic basophilia which is removable after exposure to ribonuclease. Glycogen is absent or present only in minimal quantity in apocrine ducts. Acid phosphatase and lipids are present in moderate quantities and Feulgen-positive staining of the nuclei is evident. Apocrine duct cells show no metachromasia and no alkaline phosphatase (19-21).

Apocrine sweat gland tubules possess a single type of secretory cell surrounded by a basement membrane with myoepithelium interposed (Fig. 6). The secretory cells are eosinophilic, and have a round nucleus with prominent nucleolus (Fig. 7). The nucleus occupies a basilar position in the cell. The cytoplasm of the secretory cells varies in size from a flat cuboidal type to the high columnar variety with the appearance of a pinched-off luminal tip (Figs. 7 and 8). This variation in cell height is believed to reflect the cyclic nature of the secretory process. However, no uniformity of cell height within an individual, a skin area, a single gland or tubule, can be seen, and variations in cell height are evident even in nearby cells within the same tubule. Under high power after frozen sections especially, the luminal border of the apocrine secretory cell shows a "fringe" or row of what appear to be tiny droplets (Fig. 9). These were first described by Montagna as possibly representing apocrine secretion (19). This author has demonstrated that the "decapitation" or pinched-off appearance of the glandular cell is a visual artifact. Examination of serial sections reveals that such cellular projections emanate from adjacent cells below those in the immediate surface plane of section.

The myoepithelial cells of the apocrine sweat gland are a specialized variety of smooth muscle and will be discussed in more detail in the Physiology section. They are better developed in the apocrine gland than in the eccrine gland but not so prominent as in the mammary gland. The cells are fibrillar, 40-100



Fig 7 Apocrine secretory cell Typical apocrine secretory cells [illegible] (× 1200) showing decapitation appearance of luminal tip of cell. Note pigment granules of varying size, round nucleus and prominent dark staining nucleolus (H and E)

Fig 8 Variation in height of apocrine secretory cell Section of apocrine tubules showing segments with high columnar secretory cells as well as segments with flat low cuboidal epithelium

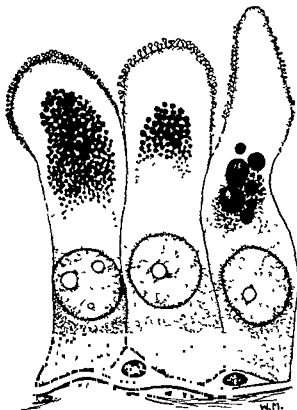


Fig 9 Apocrine secretion Drawing by Dr Wm Montagna depicting luminal fringe or droplets (o) This may be mechanism of apocrine secretion Best seen after frozen sections Luminal fringe also seen under electron microscopy (109)

microns in length and arranged so that their long axis is roughly parallel with that of the tubule They stain with hematoxylin and eosin but are seen especially well with phosphotungstic acid-hematoxylin and periodic acid-Schiff techniques (Fig 10)

The apocrine secretory cells contain numerous pigment granules which are readily visualized in an unstained section They are of



Fig 10 Myoepithelium of apocrin sweat gland Finger like projections surrounding apocrine tubules (here filled with luminal cast) are myoepithelial cells Most are cut obliquely in this section This is a PAS stain after diastase note also absence of glycogen in secretory cells of apocrine sweat gland Mag x 330

varying size and are brownish-yellow in appearance (*Fig 11*) *The number of these pigment granules varies greatly from cell to cell* Chemically these granules are in the lipofuscin family, similar to the 'abnutzung or ' wear and tear ' pigment found in the liver spleen peripheral vessels and other parts of the body They have a spectrum of properties depending on their oxidative state, showing varying degrees of sudanophilia acid fastness, reducing activity and fluorescence (20) It is this pigment which is responsible for the occasional color in apocrine sweat and in the section on chromidrosis we shall discuss it further Significantly, the ceruminous glands (apocrine glands of the ear canal) contain great numbers of these granules in the Caucasian although they are reduced in numbers in the Oriental

Histochemically apocrine secretory cells contain Feulgen-positive nuclear material ribonuclease-sensitive cytoplasmic basophilia minimal acid phosphatase (much less than in the ducts),

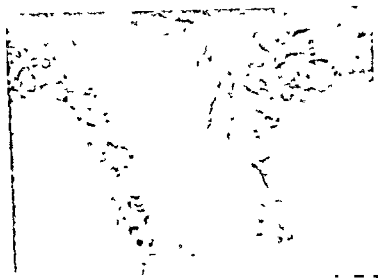


Fig. 11. Pigment granules in apocrine secretory cells. Section of unstained axillary skin showing variably sized round or irregularly shaped pigmented granules within cytoplasm of secretory cells (upper). Compare with lower photomicrograph of same section showing fluorescence of some of these granules after exposure to ultra violet light (4200 A). Mag. x 2000

and some alkaline phosphatase (19) The latter is present in the myoepithelium, also, and might in part represent diffusion from nearby blood vessels which contain great quantities of this enzyme Small eosinophilic granules of quite consistent size and supranuclear position are seen also along with a variety of lipids Bunting et al (21) described four distinct types of lipids 1 After Sudan black, a delicate gray cytoplasmic stippling probably associated with mitochondria 2 Sudanophilic droplets which give a plasmal reaction, and are acetone-insoluble, but pyridine-soluble at 60° C 3 An acetone-soluble, natural yellow pigment dissolved in the sudanophilic droplets, which emits a yellow-orange fluorescence under ultra-violet light and 4 An abundance of birefringent material soluble in acetone Montagna was unable to define clearly more than the first type described by the above authors (19) Mitochondria are present in great numbers in active apocrine tubular cells, and are most numerous near the nucleus Iron is present in many of the apocrine cells (Fig 12) especially in relation to the small yellow-brown granules The iron content of the apocrine cells shows some individual variation It is not found within the glandular lumen Mitoses are a rarity in adult apocrine glands (Fig 13), but are seen with greater frequency in "ageing" glands in elderly individuals (22) Apocrine secretory cells contain very little, if any, glycogen Montagna has found some increased amounts within inguinal apocrine sweat glands, but much less than one sees in the resting eccrine sweat gland (19) Monoamine oxidase is found in granular form in the secretory cells of the apocrine glands and similarly localized in the eccrine sweat glands (23) Succinic dehydrogenase, abundant in eccrine glands is reduced in the apocrine tubules Conversely non-specific esterase is much more highly concentrated in apocrine than in eccrine sweat glands (24) It has been suggested that these enzymes may be used to distinguish these glands when necessary as in unusual cutaneous tumors of *apparent appendageal origin* The lumen of the apocrine sweat gland may contain cellular casts or debris This is much more marked a feature after frozen sections or with freeze-drying methods, but is still evident after routine formalin fixation



Fig. 1 [illegible] pigment in [illegible] secretory cell. Dark staining material in cytoplasm of many of the secretory cells represents inorganic iron. Close study reveals it to be related to the pigment granules in the main. Note the absence of iron in adjacent cells. Prussian Blue. Mag. x 360.

Fig. 2 [illegible] of apocrine secretory cell. Mitotic figure is visible in center of photomicrograph. H[illegible]s are rare in apocrine glands. H and E. Mag. x 1370.

F. BLOOD SUPPLY—LYMPHATIC DRAINAGE

The secretory portion of the apocrine sweat gland is supplied by small arterial branches from the deep dermal arterial plexus, in the main Tiny arterioles follow and partially envelop the tubules breaking up into small capillaries The blood-filled segments of many of these vessels can be discerned on examination of the apocrine sweat glands in vivo in incised, and reflected axillary skin (Fig 3) Venules follow the course of these vessels and ultimately drain into the deep dermal plexus of veins As is true of the eccrine duct, a small arteriole and venule follow the apocrine duct as it progresses upward

In the axilla, the arterial supply is derived from branches of the subscapular and anterior circumflex humoral arteries, the axillary artery itself and occasionally from the intercostal arteries (25) This shows some individual variation Similar branches from the axillary vein carry the venous blood to the deep dermal plexus of veins We will make no attempt at description of the blood supply in the other apocrine gland-bearing areas This information is available in any anatomical text

The lymphatic drainage for all cutaneous appendages is via a plexus of vessels in the dermis just deep to the vascular plexus In the axilla, the axillary nodes receive this return sending efferent vessels to larger lymphatic vessels which empty eventually into the thoracic and right lymphatic ducts

G INNERVATION

The innervation of the human apocrine sweat gland is derived from adrenergic fibres of the autonomic nervous system Proof that this supply is of functional importance is supplied in the section on physiology

Silver stains outline these fibres poorly and suffer from the fault that they do not define nerve fibres selectively Elastic tissue and possibly myofibrils may be stained also preventing clear-cut identification of the nerve fibres As a result we could not determine the precise site of termination of the nerves supplying the apocrine sweat gland with this technique Myoepithelial elements certainly seem to be innervated but we cannot state whether or not the secretory cells are similarly supplied We could not con

firm Woolard's observation that only the myoepithelial cells of the apocrine sweat gland are innervated (26). Furthermore, we could not make out an end plate or any specialization of the nerve-endings supplying the myoepithelium, although such are commonly encountered in other muscular structures. Shelley and Cahn using a supravital technique with methylene blue confirmed these findings (27). It is noteworthy that the apocrine duct, like the eccrine duct, does not receive nerve fibres (107).

With the cholinesterase (ChE) technique (Koelle) at the usual incubation times (30, 120 minutes), we demonstrated (Figs. 14a and 14b) an absence of specific cholinesterase about apocrine sweat gland tubules (28). In contrast, the eccrine sweat glands show heavy concentrations of the enzyme. Non-specific cholinesterase was not visualized about these structures. Absence of specific ChE about the apocrine sweat gland tubules at 30, 60 and even 120 minutes incubation periods indicates that these glands are not supplied with cholinergic fibres while the eccrine sweat gland tubules which showed the presence of the enzyme, do possess this type of autonomic supply. These observations corroborate the physiologic and pharmacologic studies indicating an adrenergic innervation for the apocrine sweat gland and a cholinergic one for the eccrine gland. Interestingly, if the incubation times for the ChE technique are prolonged to four hours or beyond, some of the adrenergic fibres supplying the apocrine sweat gland will be stained. However, the staining is incomplete (Fig. 15) consistent with the very low concentrations of the enzyme in adrenergic nerves.

Although most of our studies with nerve stains were done on human axillary skin, we also examined the skin of the human ear canal in collaboration with Perry and Wood with similar techniques (29). These studies indicated an adrenergic innervation for the ceruminous glands also.

H. COMPARATIVE ANATOMY

Cutaneous glands which are anatomically apocrine in type are found in almost all mammals, although their distribution varies. In the Primates, lemuroids and platyrrhines have only apocrine glands whereas the Catarrhine monkeys also possess eccrine



Fig. 11 a and b. Cholinesterase localization in axillary sweat glands. Photomicrographs showing specific cholinesterase in nerve fibers about eccrine sweat glands at the right. This indicates presence of cholinergic innervation. Note absence of the enzyme about apocrine tubules. Upper section without counterstain. Lower section after H and E counterstain. Incubation period 30 min. Mag. × [illegible]



Fig. [illegible] *Traces of Cholinesterase in nerve fibres to apocrine glands.* Shorter incubation periods (30 min. to 120 min.) with the cholinesterase technique revealed no staining about apocrine sweat glands indicating the lack of a cholinergic innervation. Extension of the incubation period for substrate-enzyme reactivity to four hours or beyond reveals some slight irregular staining of nerve fibres about the apocrine tubules as shown above. This is consistent with an adrenergic supply. No counterstain. Incubation period 4 hours. Mag. x 360.

Fig. [illegible] *Sweat gland of dog.* Histologic section of the skin of the trunk of dog showing transected sweat gland tubules. Note resemblance of these secretory cells to those of the human apocrine gland. H. and E. Mag. x 450.

glands, though the numbers of each type varies in different species. Thus, in the macaques, the apocrine glands greatly outnumber the eccrine while in baboons, the two varieties occurred with almost equal frequency (30). The orangutang possesses both types of sweat glands in the axilla with the apocrine being more numerous (31, 32). Of the anthropoids, the chimpanzee has been studied extensively, and apparently possesses both apocrine and eccrine glands in the axilla (33). The "axillary organ" of gorillas is usually apocrine, it seems, but there may be some individual variations (30). Apocrine sweat glands are found over all of the skin surface of the gorilla except the back, palm and sole. This is not surprising in view of the well-developed terminal hair present in these animals over most of the skin surface.

Other mammals possessing apocrine type sweat glands are the dog (Fig. 16), horse, sheep and ox (34). These glands are found over most of the skin surface of these animals and, at least in the horse and sheep, are the only variety of sweat glands found. The hippopotamus apparently also possesses cutaneous apocrine glands which elaborate the well-known "bloody" sweat of that animal. In addition, apocrine glands somewhat more restricted in localization and productive of specialized colored secretions, are found in the elephant, kangaroo, gazelle, and antelope (34, 93).

We have also examined histologically the sweat glands of the horse and we shall discuss this in some detail in a later section (page 51).

It is agreed that for the most part, animal apocrine glands are quite similar, though not identical with those of man. The great majority show ducts which, as in man, empty into hair follicle orifices or quite close thereto.

Schiefferdecker has pointed out that man, representing the highest level of development, is an eccrine gland animal (6). He emphasized that apocrine glands are the more primitive, being the typical sweat glands of mammals. The anthropoids such as the chimpanzee and gorilla, appear to be closest to man in sweat gland distribution. At least they possess both types of sweat glands and in a distribution more like man than any other mammal.

III

THE PHYSIOLOGY AND PHARMACOLOGY OF THE APOCRINE SWEAT GLAND

A METHODS AND MATERIALS

FOR the most part these studies were performed on adult male volunteers However some children and women as well as clinical patients male and female were studied in certain instances as described later During the course of the various investigations several hundred men Negro and White, were used It was found necessary to screen great numbers of men in order to secure subjects who produced adequate quantities of apocrine sweat and at the same time did not have much eccrine sweating (which would be confusing and would dilute the apocrine sweat) in the area

The axilla served as the test site for the vast majority of these studies No anatomic abnormalities were present in the axillae of any of the subjects The tests were made during all seasons of the year In some subjects, antiperspirants were interdicted for at least one week prior to our observation period However in the main the axillae were merely cleansed thoroughly prior to examination to remove such material as dirt debris and old secretion

The axillae were shaved using either a safety razor or electric clipper The individual's arm was extended laterally to keep the axillary vault exposed during the observation periods Visualization of the apocrine sweat droplets was achieved with the naked eye and with an otoscope or stereoscopic magnification (2 30) Specimens were collected by means of fine capillary pipettes either placed directly on the skin surface or inserted into the hair follicle (Fig 17) Fluorescence was determined by the use of a standard Wood light

Pharmacologic agents were prepared in sterile physiological saline solution in concentrations as indicated in the specific sections In some instances, a stock commercial epinephrine solution was used, while in others, a buffered saline solution (Sørenson's phosphate buffer, pH 7 4) was employed to minimize local pain during injection Heat stress was produced by having the subjects remain in a specially constructed infrared heat cabinet for periods up to one hour

Special apparatus utilized included a Raytheon microwave (radar) diathermy unit to produce deep tissue heating, a standard electrical square wave stimulator and an electrical skin resistance recorder

It was necessary to use histologic techniques for portions of these studies also These included routine hematoxylin-eosin preparations and the phosphotungstic acid hematoxylin stain

Additional descriptive details of special methods used in certain parts of these studies will be supplied in the appropriate sections

B PHASES OF APOCRINE SWEAT GLAND FUNCTION

During our studies of the physiology of the human apocrine sweat gland we soon learned that it was possible to divide apocrine sweat gland function into two distinct phases, viz ,

Apocrine sweating, the appearance of apocrine sweat on the skin surface, and

Apocrine secretion, the actual formation of the sweat in the secretory tubules below

That there are two such distinct functional phases will become apparent as this section is read For the purposes of better organization and convenience of description we have utilized these headings at the outset

C. APOCRINE SWEATING

1. General Description

Apocrine sweat is seen to appear usually at the hair follicle orifices (Fig 18) Characteristically it is visualized as a turbid-white fluid which gradually wells up in the follicle forming a rather flat globular droplet This is in contrast with the droplet of eccrine sweat which is spherical and can be seen to emanate

from a tiny pore. Except in unusual instances, when the amount of apocrine sweat is great, or where it is diluted by eccrine sweat, spreading of the apocrine sweat droplet far beyond the follicle does not occur. This is primarily because the quantities of apocrine sweat which appear at a given follicle after stimulation are small and also because of the viscosity of the secretion. In addition, apocrine sweat dries rather quickly, forming an adherent, glistening, glue-like residue over the follicle orifice within a few minutes after appearing. This residue is opalescent and reminiscent of clear plastic or dried varnish (Fig. 18). This property is a characteristic feature of apocrine sweat and is not seen after eccrine sweating. It is not uncommon in the careful examination of the axillary skin, to find such dried apocrine sweat droplets over the follicular orifices although they are usually removed by washing and profuse sweating.

In some subjects, a fairly large number of apocrine sweat droplets may be noted at extra-follicular orifices. We found that this was more common in White subjects and was never more than 1 - 2 % of the total number of droplets seen.

While apocrine sweat is usually whitish or grayish in appearance it occasionally shows a definite yellowish tint and rarely even blue, green or black apocrine sweat may be observed (cf. Section on Localized Chromidrosis). Apocrine sweat is translucent but not transparent. However the amount of turbidity shows great individual variation (Fig. 19). In some subjects the sweat may be almost clear and identification can be made only after collection in a capillary tube and examination against a black background. In others however, commonly the Negro, the secretion may be milky-white and thick having the consistency of heavy cream. In these instances it may be impossible to collect in a capillary tube.

The total quantity of apocrine sweat produced is minute when compared with the volume of eccrine sweat which may be seen. A fair estimate of the amount of apocrine sweat produced by an individual gland in response to a given stimulus is 0.001 ml. Thus, the total quantity of apocrine sweat which can be secured from a single gland may be only a small fraction of a millili-



Fig. 19. Turbidity of apocrine sweat. Pooled samples of apocrine sweat are shown in test tube on the left. Compare with samples of pure eccrine sweat on the right. The turbidity of the apocrine sweat varies greatly from those which are milky to those which are almost clear. However, some degree of cloudiness is always evident in apocrine sweat.

The Negro produces greater amounts of apocrine sweat more commonly than does any other race, although the quantities are still relatively small.

It is important to stress that once an apocrine gland has been emptied, no further sweat may be made to appear on the skin surface until there is time for its formation in the secretory tubules below. We have repeatedly demonstrated that after any stimulus which evokes good apocrine sweating, subsequent stimulation fails to produce further apocrine sweating for a period of twenty-four to forty-eight hours. This interval is called the *refractory period* and apparently represents the time required to form a new supply of apocrine sweat. Such a finding is evidence enough that the appearance of apocrine sweat on the skin is a function distinct from the formation of the sweat itself (34).

In many of the subjects, the apocrine sweat whether dried or recently secreted, showed fluorescence when exposed to Wood light (Fig 20) Eccrine and apocrine sweat can be readily distinguished on this basis In general, increase in color tended to increase the fluorescence although dark blue and black sweat did not fluoresce at all (cf Section on Localized Chromidrosis)

2. Effect of Emotional Stimuli

Apocrine sweating was seen in response to such stresses as evoked fear or apprehension In an occasional patient on a routine clinic visit, apocrine sweating was observed This was more common in those patients apprehensive concerning the possibility of skin cancer or in those about to have minor surgery However, it was far less common than the usual emotional eccrine sweating seen under similar circumstances It was our impression that an emotional stimulus which was rather marked in intensity was *required to produce an apocrine response However, this varied* somewhat from individual to individual and in an occasional subject, apocrine sweating in response to emotional stimuli appeared more readily than an axillary eccrine response

Seventeen patients were examined prior to being subjected to a lumbar puncture These people were all admittedly fearful of the procedure and most had questioned us regarding its dangers In four of these individuals axillary apocrine sweating was observed This compares favorably with a series of observations on consecutive clinic patients in whom two out of fifteen exhibited apocrine sweating

Another study of the effect of apprehension or fear was conducted on thirty-three experimental subjects These men were entirely unaware of what experimental procedures might be conducted and many of them showed distinct apprehension However, only *five of the thirty-three showed axillary apocrine sweating* prior to testing

It was not possible to study the apocrine response following other forms of emotional stimulation such as sexual stimulation or anger However it is probable that the response to these stimuli would correspond with that described above after fear-producing stimuli



Fig. 70 Fluorescence of apocrine sweat droplets Three small droplets of apocrine sweat were placed on a glass slide. Upon exposure to Wood light (UVL 3660 A) the fluorescence shown above was seen.

3 Effect of Sensory Stimuli

It was found that rather severe *pain* was required to elicit apocrine sweating. In the series of observations on seventeen patients having a lumbar puncture, three of these individuals showed apocrine sweating immediately following pain produced by the puncture. The application of an electrically heated wire to the skin of the back produced apocrine sweating in two of eleven subjects studied. Radiant heat which was focussed on a small area on the forearm 1 inch in diameter was used as a painful stimulus in two subjects. In both, severe pain was produced and apocrine sweating resulted. In twenty five subjects a No. 18 needle was inserted into the palm to produce pain. Apocrine sweating was observed in ten of these subjects.

The effect of pain in the production of apocrine sweating was beautifully illustrated in women during labor. It was found that mild uterine contractions were not associated with an apocrine response. However, intense contractions producing severe pain could be correlated with apocrine sweating. Within a few seconds

after the onset of each intense labor pain, six to ten apocrine sweat droplets appeared. Observations over a period of one hour indicated that each burst of apocrine sweating involved new glands. Secretion did not reappear at former sites of activity.

It was found possible to block the apocrine sweat gland response to pain by the introduction of procain into the axillary skin. Sixteen subjects received an injection of 4% aqueous procain intradermally. Five to ten minutes later, after local anesthesia in the axilla had been produced, the sixteen subjects received a painful stimulus consisting of the introduction of a needle into the palmar skin. In four of these, apocrine sweating was visualized in the unanesthetized control zones. In none of these subjects was apocrine sweating evident in the anesthetized areas. A similar local inhibition after procain was produced following emotional stimulation.

The *apocrine response to pain was further studied by the use* of a localized external pressure which obliterated the circulatory supply. A pressure of 225 mm. of mercury was applied to a small area of axillary skin of fourteen subjects using a cup device, with *an attached sphygmomanometer. Control observations had shown* that this pressure did not produce apocrine sweating nor did it diminish an apocrine response in any. The fourteen individuals were given a painful stimulus consisting of the introduction of a *needle into the palm. In five of the fourteen subjects, apocrine* sweat was noted in the normal control areas (outside the pressure zone). In four of the fourteen subjects, apocrine sweat was noted simultaneously in the pressurized areas. The apocrine sweat *response to pain appeared within one second and was generalized* throughout the axillary region unlike that to be described in response to drugs and other local stimuli (35).

It should be emphasized that the apocrine responses to emotional and sensory stimuli appeared *within one second and were generalized* in nature. They involved potentially all of the apocrine sweat glands of the axillae unlike that to be described in response to drugs and other local stimuli. In this regard we often noticed responses from apocrine sweat glands of the mammary areola, the pubic area and from occasional glands of the trunk as well as the axillae after the above emotional and sensory stimuli.

4. Effect of Heat

***(a) General*:** Nineteen subjects were placed in an infra-red cabinet for periods of approximately thirty minutes. Apocrine sweating was seen in only one of these subjects as a result of this heat stimulus, although profuse eccrine sweating was observed in all subjects. Interestingly, most of these subjects showed "follicular" eccrine sweating. That is, the eccrine sweat appeared to originate from the follicle. This was quite prominent in the axillae and the thighs. Capillary tubes were placed in the follicular orifices of five of these subjects and it was impossible to demonstrate the secretion of any apocrine sweat. The one subject in whom apocrine sweat was observed during heat showed definite signs of anxiety and apprehension, and it was assumed that his apocrine sweating was on the basis of an emotional stimulus rather than the thermal one.

(b) Local ("Deep") Heat Four healthy adult males were used in this study. In a room at 22° C., these men had their axillae shaved and were placed at rest. No apocrine sweating was seen at this time. Deep heat was applied to the axilla using a microwave (radar) diathermy machine with a corner reflector for twelve minutes. In all four subjects studied, definite apocrine sweating was seen between five and ten minutes after the application of the heat. While minimal in amount, the secretion was readily identified. It is to be stressed that the subjects experienced only slight warming of the skin (1 – 2° C. elevation by thermocouple determination of external skin temperature). However the skin temperature of the subcutaneous tissue was elevated between four and five degrees (41 – 42° C.). The control zone, the focussed area which received the largest amount of heat contained 90% of the apocrine sweat droplets.

5. Effect of Cold

(a) General Five subjects were examined for apocrine sweating before and upon removal from a cold room (—40° C.). These men had been fully clothed in Arctic wear and were lying at rest on a non-conducting bed for forty-five minutes. The temperature of the axillary skin fell about 3° C. (to 34° C.) during this period. All of these subjects seemed to be apprehensive upon removal

from the cold room No fresh or dried axillary apocrine sweat was observed when these subjects were examined on removal from this environment Unfortunately, we did not have the opportunity to use drugs or other stimuli in an effort to induce apocrine sweating

(b) Local ("Deep") Cold: Deep cold was applied to the axilla in such a manner as to effect structures at a deep dermal and subcutaneous level The shaved axillae of four healthy adult male subjects were procainized in a block technique leaving a central area free from the pressure effects of the procain An 18 gauge needle was inserted 3-4 mm beneath the skin surface adjacent to a hair follicle in the central zone Frequently, some mechanically stimulated apocrine sweating could be seen This was minimal in amount, however, and was allowed to subside so that after 2-3 minutes following the insertion of this large needle a chilled 20 gauge needle was inserted into the same hole This 20 gauge needle, two inches in length, was placed through the tip of a 30 cc syringe The needle hub remained within the barrel which was then packed with dry ice In a 2-3 mm zone immediately around the needle, no apocrine sweat could be visualized However at the periphery of this zone, small amounts of apocrine sweat could be visualized It is probable that a temperature gradient was present and that in this central zone where the temperature was coldest paralysis of the gland occurred A suitable temperature was reached however in the tissue at a 3-4 mm distance

6 Effect of Seasonal Variations

Apocrine sweating was studied in over forty subjects during all seasons of the year Unlike eccrine sweating which was greater during the summer months we were unable to detect an appreciable change in the quality or quantity of apocrine sweat seen during the various seasons We have not had an opportunity to examine the effects of acclimatization to heat and cold on the apocrine sweat gland responses

7. Effect of Drugs

(a) Adrenergic In twenty-five male subjects, epinephrine in a 1 1000 concentration in sterile saline solution was injected

intradermally The quantities injected varied from 0 01 cc to 0 10 cc In each of the twenty five subjects, apocrine sweating appeared usually at follicular orifices, although a few extra-follicular droplets were seen in some of the men The larger quantities of the drug produced stimulation of more glands since there was a greater spread of drug A latent period, representing the time required for spread of the drug and reactivity of the gland was seen and was never less than fifteen seconds The average latent period was 30 secs although in some instances it was as high as 120 seconds The response continued for a period of from five to ten minutes with an ever-widening zone in which glands began to show activity The active glands were almost invariably located in the zone showing blanching from the epinephrine This was an indication of direct pharmacologic stimulation of the glands

It was possible also to produce apocrine sweating by the systemic administration of epinephrine In these cases, it was necessary to give rather large doses of the epinephrine Apocrine sweating was not seen until systemic signs of the drug were also evident It could usually be produced by the hypodermic injection of 1 0 cc of 1 1000 solution of epinephrine

The local introduction of nor-epinephrine (levo-phed bitartrate, 0 05 cc of 1 1000 solution) in seven subjects also induced apocrine sweating in all of them

The use of epinephrine (1 1000) in a buffered solution (ph = 7 4) in an effort to minimize local pain, in ten subjects also produced an apocrine response corresponding to what was described above after epinephrine in saline

Epinephrine in dilutions from 1 10,000 to 1 1,000,000 were also employed to stimulate apocrine sweating The response was less consistently produced in the higher dilutions, above 1 500,000

(b) *Cholinergic* Freshly prepared acetylcholine 0 05 cc of 1 1000 aqueous solution was introduced intradermally in the axillary skin of ten subjects In none of these was true apocrine sweating observed However "follicular" eccrine sweating could be seen

Weaker dilutions 1 100 000 of the drug were also used without production of an apocrine response

Pilocarpine (0 05 cc of 1 1000 sterile buffered saline) was injected intradermally in the axilla of twenty-five subjects In three of these, true apocrine sweating was seen In twelve of them clear "follicular" eccrine sweating was observed Normal eccrine sweating was seen in all of the subjects

Physostigmine (1 10,000 in sterile buffered saline) was injected intradermally in the axilla of four subjects Apocrine sweating did not occur in any of these, but an eccrine response was readily visualized in all four

***(c) Anti-adrenergic*·** The administration of Dibenzyline[®] (20 mg) prevented subsequent axillary apocrine sweating in response to 0 15 cc , of 1 1000 local epinephrine in two normal adult male subjects A blood pressure drop and reduction in pulse rate was observed in each indicating systemic effect

Local inunction of Dibozane hydrochloride,[®] a potent anti-adrenergic found to be effective when applied locally in animals was used in three adult male volunteers The concentration of the drug was 50 mg Gm of ointment (polyethylene glycol 4000) and effort was made to rub the ointment into the skin After two such applications one hour apart 0 15 cc 1 1000 epinephrine in normal saline was injected into the treated axillary skin Apocrine sweating was observed in all of the subjects with no evidence of inhibition There was no vasodilatation in the dibozane-treated skin and no inhibition of vasoconstriction to epinephrine

Ergotamine tartrate which blocks some adrenergic responses after local administration did not inhibit epinephrine-induced apocrine sweating in three male subjects in whom it was attempted Dosage used of the ergotamine tartrate was 0 1 cc 1 1000 solution

(d) Anticholinergic The local injection into axillary skin of 0 10 cc of atropine solution (1 1000) failed to produce apocrine sweating in nine male subjects Subsequent introduction of epinephrine (0 1 cc 1 1000) into this atropinized area produced apocrine sweating in all of the subjects studied

Systemic administration of atropine was not employed

However Prantal[R] administered orally in 100 mgm tablets (2-6 tablets q i d) to five normal adult male subjects did not produce inhibition of apocrine sweating after epinephrine Reduction in eccrine sweating was noted only after signs of systemic

effects of the drug Prantal ointment was also without effect on apocrine or eccrine sweating in the axilla

(e) Local Anesthetics In sixteen subjects, a small area of axillary skin was anesthetized by the local injection of 1 0 cc of 4% procain solution Epinephrine given into the normal un anesthetized areas produced apocrine sweat in all sixteen In the anesthetized areas apocrine sweating was produced after epinephrine in 15 of the 16 subjects

It is to be recalled that the response to emotional and sensory stimuli can be blocked with local procaine (see page 34)

(f) Antispasmodics—Smooth Muscle Relaxants *Papaverine nitrate*, 2-10 mgm in 0 2 cc normal saline, was injected intra dermally in the axillary skin of three subjects Subsequent injection of 0 05 cc of 1 1000 to 1 100,000 epinephrine produced apocrine sweating in all three

In a similar series of experiments utilizing *sodium nitrite*, a so called relaxant of smooth muscle, we were unable to inhibit apocrine sweating to epinephrine Subcutaneous administration of 0 1 cc of 1 1000 solution of sodium nitrite brought about prompt vasodilation Subsequent injection of 0 1 cc of 1 1000 to 1 300 000 epinephrine then produced blanching in this same area and as the blanching developed areas of apocrine sweating appeared It is felt that the action of epinephrine was more pro nounced and because of its high potency, overcame the original relaxant effect of the nitrite

(g) Effect of other Drugs *Pitocin* the oxytocic principal of the posterior pituitary which contracts uterine musculature so charac teristically will also produce copious apocrine sweating The subcutaneous injection of various strengths of pitocin varying from 0 1 to 1 international unit produced such a response in each of 30 male subjects Injection of 0 01 international unit produced apocrine sweating in 21 of 30 individuals studied

Histamine which is also a consistent stimulant for many varieties of smooth muscle was injected subcutaneously in nine healthy adult male subjects The phosphate salt was used in a concen tration of 1 10 000 True apocrine sweating was observed in only one of these nine individuals Histamine urticaria developed in all nine



Fig 21 Manual expression of apocrine sweat A fold of axillary skin is manually compressed between two fingers Ap[illegible] s[illegible] droplets [illegible] appeared at several of the hair follicle orifices

The effect of *nicotine* on apocrine sweating is discussed below in the section on axon reflex apocrine sweating

8 Effect of Physical Stimuli

Apocrine sweat may be *manually expressed* from the axillary skin Compression of the axillary skin in a gentle sliding action resulted in the appearance of apocrine sweat at follicular orifices in all of sixty subjects studied Apocrine sweat was not seen at all of the follicular orifices of the compressed skin however (Fig 21) Apparently these glands had been emptied a short time previously from some other stimulus Thus in the absence of any secretory stimulation one may instantly express apocrine sweat by simple manual compression of the axillary skin *This would indicate that* such sweat is preformed and is pooled in the tubular lumen awaiting an expulsive evacuating force As we shall learn later this force is supplied by the myoepithelium

Stroking of the axillary skin with a tongue blade will in some subjects produce a linear response in the zone of stroking This

phenomenon is discussed in more detail later (page 47) and apparently results from a mechanical stimulation of the myoepithelium

9 Effect of External Pressure

Using a glass cup apparatus attached to an aneroid sphygmomanometer by means of a side arm, it was possible to subject a localized area of the axilla to high external pressure. In five subjects, it was determined that the application of this pressure did not stimulate any apocrine sweat gland activity The following experiment was then conducted Epinephrine (0 15 cc of 1 1000) was injected intradermally Within 1 to 2 seconds, a pressure of 225 mm (plus or minus 10 mm) of mercury was applied to the injection site and maintained for three minutes During this period apocrine sweating was observed in the pressurized area, but not in the surrounding zone However, within a minute after removal of the pressure, apocrine sweating could be seen to appear in the surrounding skin This was presumably due to lymphatic spread of the epinephrine, which had been previously prevented by the pressure of the rim of the cup

10 Effect of Natural Factors—Age, Sex, Race

Eleven children ages five to ten years were studied for apocrine sweating The group comprised three Negro boys, three Negro girls three White boys and two White girls Each was given 0 05 cc of 1 1000 solution of epinephrine intradermally in the axillary skin In none of them was apocrine sweating visualized A pain stimulus also was given to each of the children This consisted of the introduction of a hypodermic needle, No 25 gauge into the skin of the forearm Again no apocrine sweating was seen It should be pointed out that none of these children had axillary hair other than the lanugo type

Thirty five normal healthy adult males (19 White 17 Negro) ranging in age from 15 to 50 years were also examined Each of this group was given a painful stimulus by means of the introduction of a No 18 needle in the palm Fourteen of these individuals (of whom 8 were Negro) showed apocrine sweating after this stimulus These subjects also were studied after 0 15 cc of 1 1000 epinephrine was introduced into the skin of the axilla

Definite apocrine sweating was seen in each of the thirty-five subjects. However, the degree of response showed marked variation.

An older age group was also studied. This consisted of 11 male subjects (8 White, 3 Negro) ranging in age from 60 to 75 years. The pain of the palmar injection produced axillary apocrine sweating in three of the 11 men (all White). Each of them also received an intradermal injection of 0.1 cc of 1:1000 epinephrine in the axilla. Six of the eleven subjects developed apocrine sweating in response to this drug.

Limited studies were also made, with similar findings, on the apocrine response in female subjects. Five women varying in age from 23 to 38 years were examined for apocrine sweating after local epinephrine and pain. The response was less than that seen in adult males of the same age group.

Racial variations in apocrine sweating are remarkable. Comparison of thirty Negro and thirty White adult male subjects after local epinephrine and emotional stimulation revealed that the Negro consistently produces greater quantities of apocrine sweat than does the White. In addition the apocrine sweat of the Negro generally showed more turbidity and was elicited more readily after minor stimuli, such as produced by stroking. These features also reflect the racial superiority of the Negro. Various groups within the Caucasian race showed no significant variations. We have not had the opportunity to study Oriental or Indian races for apocrine sweating.

11. The Refractory Period—Miscellaneous Observations

It was pointed out earlier that the individual apocrine gland has a definite refractory period. After the initial injection of epinephrine it is impossible to produce apocrine sweat from any unit which has responded until a period of hours have elapsed. The exact duration of this period always exceeds twenty-four hours and varies from individual to individual, even from gland to gland. In general Negroes, with larger glands, tend to have shorter refractory periods. The maximum duration of this period is about 72 hours.

No spontaneous apocrine sweating was observed in subjects at rest. One individual had capillary pipettes placed in the follicular

orifices, and during a period of three hours, no fluid or follicular secretion could be seen to enter these pipettes, nor was any dried apocrine sweat seen At the end of this period, 0 15 cc 1 1000 epinephrine was injected intradermally into the observed axilla and a typical apocrine response noted

Apocrine sweat never appeared at all hair follicle orifices in response to a given stimulus In one such study, 63 hair follicles were observed following local epinephrine Sixteen glands were activated, 14 of these being follicular, whereas 2 were extra-follicular

In five adult male volunteers, we also studied the electrical skin resistance (E S R) of the axillary skin Each of these subjects was carefully selected on the basis of his ability to produce an adequate apocrine response and failure to show emotional or sensory axillary eccrine sweating The axillae were shaved and cleansed carefully The axillary skin was moistened with a wad of cotton saturated with normal saline A small hole was cut in the cotton just large enough for the metal electrode (0 5 cm in diameter) A base line electrical skin resistance (resistance to the passage of direct current, thus not a measure of impedance) reading was taken in the axilla Normal saline was constantly dropped onto the cotton to insure its saturation Following this 0 10 cc of pitocin was injected into the axillary skin to induce apocrine sweating In four of the five subjects, the E S R showed no change from that of the previous pre-stimulation level In one subject a decrease of 2 ma from the base line E S R was recorded This subject showed no outward manifestation of pain or apprehension at the time Ten minutes later after apocrine sweating had ceased another "saturation baseline reading was taken and found to be within 1 ma of that taken before the injection of pitocin 0 1 cc of 1 1000 pilocarpine was then introduced into the axillary skin to induce eccrine sweating Within 10 seconds the E S R was seen to fall an additional 4 to 7 ma and even 10 ma lower in one subject This lowered E S R was maintained for 10 to 30 minutes apparently as long as the eccrine sweating continued

Darrow in ingenious experiments, using a "wet" electrode technique has shown that the drop in E S R seen after eccrine

sweating is not merely the result of adding fluid to the skin surface, but results from a change within the skin apparently related to the active eccrine secretory process per se (36)

It is noteworthy that Lobitz and Campbell in studying the apocrine wax glands of the ear canal also found no drop in skin resistance as a result of apocrine stimulation while they did record the usual drop in the E S R of the palmar skin simultaneously (37) These findings are in agreement with ours and lend support to the concept that no active cellular secretion occurs at the time of apocrine sweating

12 Axon Reflex Apocrine Sweating

Efforts were made to induce apocrine axon-reflex sweating, heretofore not demonstrated in man In thirty experiments on fifteen adult male subjects, utilizing appropriate concentrations (1 50,000 to 1 150,000) of acetylcholine and nicotine salts introduced iontophoretically or by local injection, we were unable to produce the instantaneous, wide area response characteristic of the axon-reflex While distant glands were activated the response was irregular and inconstant This may have been due *in part to the long refractory period (24-48 hours) following a* bout of apocrine sweating It is practically impossible to prevent some apocrine sweating since many emotional and physical stimuli may prompt its occurrence thus emptying some or many of the apocrine sweat glands While the anatomic and physiologic evidence of the innervation of this gland suggests that apocrine axon-reflex sweating should occur, we were unable to demonstrate the phenomenon to our satisfaction In this regard, it is interesting to note that Aoki using appropriate concentrations of nicotine and acetylcholine, could not induce axon-reflex sweating in the dog except in certain restricted areas (38) It should be recalled that the dog possesses a *sweat gland which at least by histological* criteria, is apocrine in type

13. Mechanism—Role of the Myoepithelium

Earlier we described the well-developed band of smooth muscle which invests the tubular portion of the apocrine sweat gland This layer of cells has been called *myoepithelium* and is seen also in the eccrine and mammary glands in varying degrees of



Fig. 22. Myoepithelium of apocrine gland. Phosphotungstic acid hematoxylin stain of axillary skin showing myoepithelium in transverse, oblique and longitudinal planes of section. Mag. × 750

development. We have pointed out in recent pages, the need for a contractile force to empty the apocrine tubules and thus produce apocrine sweating. It is the myoepithelium which provides this force. All of the physiologic and pharmacologic phenomena concerned with apocrine sweating reflect the reactivity of this band of smooth muscle.

It is our purpose then in this section to carefully review the evidence already presented indicating that such a mechanism exists and to present additional corroborative data which prove it (39).

a. Anatomical Evidence. The histologic findings suggest that myoepithelium is smooth muscle. It is a well developed fibrillar layer of myoid cells which is present about the secretory portion of the apocrine sweat gland but absent about the duct. Individual myoepithelial cells are almost *linear or spindle-shaped (Fig. 22)* and show cytoplasmic branching in rare instances. They have an average width of 8-10 microns and reach a length of 40 to 100 microns. An elongated basophilic nucleus can be visualized near the mid portion of the cytoplasm.

The arrangement of the myoepithelial cells is suggestive functionally for they run longitudinally with their long axis roughly parallel with that of the apocrine tubule. Large sheets of these fibril-like cells may be seen on routine sectioning if the tubule is cut longitudinally (Fig 22)

Although the myoepithelial cells take some muscle stains poorly, a fact which has led some histologists to exclude them as plain muscle, they are easily visualized under routine hematoxylin and eosin preparations or with the periodic acid-Schiff procedure However, they stain more completely with the phosphotungstic acid-hematoxylin stain as blue fibrils in contrast with brown tubular cells Under high magnification a faint longitudinal striation may be seen When examined with proper illumination, the myoepithelial cells exhibit a birefringence which is positive with respect to the long axis of the cells This indicates the presence of longitudinally arranged rodlets or fibrils (21) Such a property is common to smooth muscle in general

Woolard has stated that the *innervation* to the apocrine sweat gland is to the myoepithelium exclusively As mentioned earlier, we would agree that these cells do receive fibres although we are unable to state categorically that the secretory cells are not also innervated

An attempt was made to secure some indication of myoepithelial function by studying its appearance before and during apocrine sweating Biopsies were secured from the axillae of five normal subjects Procain block anesthesia was used to minimize pressure effects on the histologic appearance Similar biopsies were secured from five subjects in whom apocrine sweating had been induced 3-4 minutes previously by the local injection of epinephrine All biopsy material was sectioned serially and stained with hemotoxylin and eosin Comparison of the sections from the two groups did not reveal any consistent morphologic differences No evidence could be obtained from these studies which would support or refute the view that myoepithelium is contractile Failure to provide evidence with this study is apparently due to technical difficulty, primarily the inability to prevent some myoepithelial activity from non-specific stimuli encountered in the study However, many segments of apocrine tubules of "unstimulated"

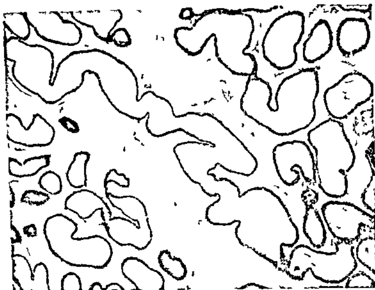


Fig 23 Peristaltic wave in apocrine tubules Chance sectioning of rather long stretch of an apocrine tubule showing multiple compression and dilatation along its course These glands were not purposely stimulated Changes seen are reminiscent of peristaltic wave as seen in the G I tract H and E Mag x 310

glands after routine staining show changes which could be easily interpreted as contraction (Fig 23)

b Physiologic & Pharmacologic Evidence The fact that apocrine sweat, in the complete absence of any other stimuli, may be manually expressed, as described earlier, is a strong indication that a contractile force is required to deliver the apocrine sweat to the skin surface Furthermore, the induction of apocrine sweating by stimuli selective for smooth muscle suggests that a contractile force is responsible for sweating These stimuli are as follows

(a) *Mechanical stimulation* of the axillary skin will result in the appearance of apocrine sweat on the skin surface In fifteen healthy adult male subjects, the shaved axilla was firmly stroked in a linear fashion 10-15 times Within 20 seconds, a linear band of apocrine sweat was seen in the zone that had been stroked in nine of the 15 men (Fig 24) The amount of sweat produced with this stimulus was small when compared with the quantity



Fig 21 Apocrine sweating after stroking axillary skin After lightly stroking the axillary in a linear fashion with a tongue blade 10 15 times a linear band of apocrine sweat was seen in the area stroked as shown above This is the result of physical stimulation of the myoepithelium

seen on other occasions in these individuals It should be noted that the stroking was not overly forceful and that no compression or excessive stretching of the axillary skin was seen It was felt that apocrine sweating following stroking of the axillary skin occurred as a result of mechanical stimulation of the myoepithelium surrounding the apocrine tubules

In three subjects in whom half of the axilla was anesthetized with procain (4%) anesthesia, stroking across the normal control area and the anasthetized zone produced the same effect The apocrine sweating was sharply delineated to the area of stroking Both of these observations suggest that the sweating was not induced by neural stimulation

(b) *Thermal stimuli*, such as *heat* or *cold*, when properly applied at a deep level so as to produce actual thermal stimulation of the myoepithelium can induce apocrine sweating These experiments were described earlier in the Physiology chapter (pp 35-36)

It should be stressed that this is an artificial mode of stimulation and one that is very unlikely under physiologic conditions

It has been previously shown that the external application of heat and cold, as would be produced in a hot box or a cold room, would not generate an apocrine response apparently because there is no myoepithelial stimulation

(c) *Electrical stimuli*, when applied directly, also prompt apocrine sweating apparently through direct electrical stimulation of the myoepithelium The use of a square wave stimulator with a needle electrode allowed for unit gland stimulation Five healthy adult males were studied The axillae were procainized in a block technique as previously described The active electrode was then inserted into the axillary skin During the two minute interval following insertion some apocrine sweating was occasionally seen as a result of mechanical stimulation This was allowed to subside and then the square wave current was applied The voltage applied ranged from 0 1 to 28 0 v, frequency was 50 to 200 pulse and the pulse duration 0 1 to 3 0 milliseconds Definite though not pronounced apocrine sweating in the form of a unit gland response was seen in all subjects

(d) *The pharmacologic stimuli* which produce apocrine sweating will also prompt contraction of other varieties of smooth muscle

Epinephrine and *non epinephrine* have been shown to be powerful pharmacologic stimuli for the apocrine sweat gland These drugs stimulate a wide range of smooth muscle such as the dilator muscle of the pupil of the eye and the smooth muscle around blood vessels

Pitocin the oxytocic principal of the posterior pituitary which stimulates uterine musculature will also produce copious apocrine sweating as described earlier Pitocin similarly stimulates myoepithelial contraction in the mammary gland and accomplishes the let down of milk (108)

Histamine however is apparently not a stimulus for the myoepithelium of the apocrine sweat gland since it did not produce apocrine sweating consistently It is well known however that this drug will stimulate many types of smooth muscle

c Direct Visual Evidence of Contractile Mechanism Attempts to observe the effects of myoepithelial contraction in vitro were

uniformly unsuccessful. After removal of thin strips of axillary skin and subsequent immersion in warm oxygenated mammalian saline solution, we were unable to detect any tubular changes which might indicate myoepithelial contraction. In view of our failure with this approach, an in vivo technique was tried for an intact nerve supply is a requisite for the proper function of certain types of smooth muscle.

The axillae of five selected subjects were procainized and slightly curved incisions, approximately 1½ inches long, made. Little attempt was made to control blood flow except for mild compression temporarily. One edge of the incision was everted with Allis forceps. The other edge was depressed and the apocrine glands then readily observed through a stereoscopic microscope (30 x magnification). No staining of the tissue was necessary. The addition of a few drops of epinephrine (1:1000 solution) *prompted peristaltic waves in the apocrine tubules of two of the subjects.* However, two or three drops of full strength pitocin solution initiated similar wave motions in the tubules of all of these subjects. These contractile changes were more readily elicited and seemed more vigorous after pitocin than after epinephrine. Electrical stimulation as well as the direct application of heat or cold was not attempted.

It is to be emphasized that the peristaltic wave like changes in the apocrine tubules coincided with the appearances of apocrine sweat at the skin surface. These waves are schematically illustrated in Figure 25. They are gentle, delicate constrictive changes which progress smoothly and rather slowly along the tubule to result in evacuation of the gland. No extreme segmental contractions were seen as are common in the small bowel. However, it was possible to detect vermiform movements in the bulk of the gland itself. These were thought to represent the gradual progression of the peristaltic waves along the tubules. It should be noted that *in order to see such changes in tubular lumen* it is necessary to concentrate on a small segment of the tubule. High magnification and critical illumination are essential. In addition, not all of the glands seen during these studies were responsive to stimuli. Although the blood supply to these glands appeared to be excellent during the entire procedure, perhaps the glands themselves

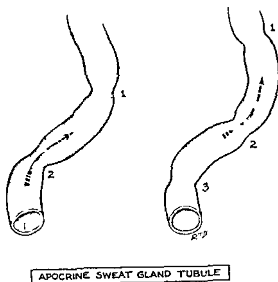


Fig 2. Peristaltic waves in apocrine tubule Schematic drawing of apocrine sweat gland tubule showing progression of peristaltic wave

or innervation of some of the glands had been damaged during the actual incision

The array of evidence thus presented provides us with more than adequate proof of the contractility of the apocrine myoepithelium This same myoepithelium has been shown to function similarly in the mammary gland, providing the "let down of milk" in response to the same drugs In the eccrine gland, however, where a less well-developed myoepithelium prevails, no real evidence of myoepithelial activity is available Eccrine sweating can be explained satisfactorily on the basis of its secretory activity

14 Comparative Studies

Our studies in other animals have been significant, although limited and supply us with cogent data with which to compare mammalian apocrine function

The *horse* is one animal we had the opportunity to observe carefully The sweat gland of this animal is more "apocrine" than "eccrine" anatomically while having some of the features of both glands First the horse sweat gland is found over most of the skin

surface as is the human eccrine sweat gland, and is not restricted in localization as is the human apocrine sweat gland The overall size of the individual sweat gland in the horse is considerably smaller than the human apocrine gland, but larger than that of the eccrine sweat gland (Fig 26) However, when one compares the overall body size of this animal with that of man, perhaps the horse's sweat gland is proportionately equivalent to that of the human eccrine gland It appears that the sweat glands in certain cutaneous areas are somewhat larger than on the general skin surface This is true about the anus for example, but it is equally true that eccrine glandular size in man will vary somewhat from region to region The palmar sweat glands in man are comparatively large, for example Histologically, we are again faced with a dilemma for the horse s sweat gland again appears to be intermediate The tubular diameter is small, consistent with that of the eccrine sweat gland in man (Fig 27) However, only one type of secretory cell may be seen as in the human apocrine sweat gland and unlike the eccrine tubule which shows two distinct types of secretory cells In addition the secretory cells of the horse s sweat gland show what appears to be decapitation secretion the pinched-off luminal buds characteristic of an apocrine type of secretion It should be stressed, however that luminal casts occasionally seen in the human apocrine gland but not in the eccrine were not evident in the sweat glands of the horse

We decided to extend our comparative studies to physiology and pharmacology in an effort to determine the nature of the horse sweat gland Two healthy mature animals were used for this study through the co-operation of Dr F Kral of the School of Veterinary Medicine University of Pennsylvania Philadelphia Pa The following stimuli were employed to stimulate sweating

(1) Hot room 100° F
(2) Exercise
(3) Manual expression of sweat
(4) Stroking with tongue blade
(5) Epinephrine (1 1000 and 1 100 000)
(6) Acetylcholine (1 1000 and 1 100 000)





Fig. 3. *Horse sweat gland.* Photomicrograph of skin from the trunk of a horse. Sweat gland tubules are visible in the corium. H and E. Mag. x 200.
Fig. 2. *Horse sweat gland under high power.* Photomicrograph of sweat glands of tail skin of horse. Note single type secretory cell, absence of luminal cavity. H and E. Mag. x 500.

Direct visualization of shaved (and thoroughly cleansed) and unshaved areas of skin was employed Areas studied included the neck, axillae, trunk (side), and extremities

It was found that the sweat glands of the horse respond to heat, exercise, epinephrine (both concentrations) and acetylcholine (both concentrations) However, stroking of the skin did not elicit a response nor could any sweat be expressed manually It should be stressed also that the sweat gland of the horse has no *refractory* period as does the human apocrine gland The horse sweat gland continues to secrete until the stimulus ceases Furthermore, the turbidity ascribed to horse's perspiration is apparently due to contamination with dander While unshaved areas showed turbid sweat, the shaved skin which had been thoroughly cleansed showed clear watery "eccrinoid" secretion Evans and Smith have demonstrated also that the horse sweat gland responds to both epinephrine and acetylcholine, as well as heat Interestingly they were unable to inhibit the thermal sweating with atropine (41)

Through the courtesy of Dr Herbert Ratcliffe Curator we had the opportunity to observe the secretion of "bloody" sweat by the huge hippopotamus Jimmy at the Philadelphia Zoo This slimy, mucoid reddish secretion appears in response to emotional stimulation such as anger or fear The animal's dislike of his handlers is so intense that we were able to provoke him quite readily by having one of these men approach him Areas which seemed to show the greatest response were the face (forehead region) and rostral back We were unable to stimulate the animal with drugs or other stimuli because of the risk involved The glands responsible for this secretion are purportedly apocrine in type (34) The similarities of the sweat of the hippo (its turbidity viscosity and color) as well as the responsiveness of this gland to emotional stimuli would fully support this

We also examined the pygmy hippopotamus a different species from South America under similar conditions This animal did not secrete a colored sweat, but did produce a frothy, white product when angry or frightened over the trunk and neck

A large gorilla tightly caged because of violence was observed Although his fur prevented identification of any cutaneous secre-

tion the strong, acrid body odor of the animal was quite apparent

Dogs possess apocrine glands over most of the skin surface These glands do not usually respond to heat, but will be activated when the thermal stimulus is excessive, suggesting that an associated emotional stimulation is brought into play (42)

Sheep, like horses, possess apocrine glands over most of the skin surface which secrete large quantities of a clear fluid Like the horse, the sweat glands are apocrine histologically, but eccrine physiologically, at least in many respects

A number of other animals possess special localized skin glands which produce colored or odoriferous secretions in response to fear or anger-provoking stimuli (34) The skunk and musk ox are prime examples In addition, the elephant elaborates a blue fluid from a gland near the eye when angry Kangaroos secrete red sweat, antelopes and gazelles a blue or blue-black sweat when frightened These originate from tubular glands which have apocrine characteristics

It is indeed interesting and informative to compare the function of the sweat glands of these various mammalia Yet one should be hesitant in the extension of interpretations from one species to another Study of the horse and human sweat glands is an excellent example in point A tally of the properties of the horse sweat gland will reveal that it is more like the human eccrine gland functionally than the human apocrine gland, although we still generally regard it as intermediate between the two Yet because of the histological appearance of the secretory cells the horse sweat gland is usually thought of as an apocrine gland This points up not only the folly of basing interpretations of functional activity on anatomical evidence but also the danger of using comparative data to draw conclusions regarding functions in another animal such as man While such evidence is helpful and corroborative it should be considered only in light of all of the available evidence

15 The Problem of Two Secretions

Herrmann has described axillary apocrine sweating in response to heat and acetylcholine (43) Furthermore Rothman has added that the human apocrine sweat gland is apparently capable of producing two secretions, totally different in appearance and

resulting from totally different stimuli (40) One secretion a viscid, turbid-white liquid appears at hair follicle orifices following *emotional* (fear, anger), *sensory* (pain), *mechanical* (stroking) and *pharmacologic* (epinephrine, pitocin) stimuli This fluid does not appear in response to heat, and cannot be inhibited by atropine Moreover, it can be produced by simple, manual compression of the axillary skin It is probable that all observers, including Herrmann and Rothman, will readily agree that this secretion is apocrine in origin However, a second secretion, a clear, colorless, watery fluid will also appear to emanate from the same hair follicle orifice in response to *heat* and *cholinergic* (acetylcholine, pilocarpine) drugs Atropinization of the areas prevents the appearance of this fluid It is this product which the above authors feel is derived from the apocrine sweat gland We have examined the problem in detail and have concluded that the human apocrine sweat gland produces only one secretion the viscid turbid white sweat The clear, aqueous, "follicular" fluid is in reality eccrine sweat which arises from adjacent eccrine sweat duct pores and collects at the follicular orifices giving a false impression of its origin

At the bottom of this problem is the fact that simple inspection even with stereoscopic magnification (30 x) does not enable one to identify the points of origin of these secretions Additional evidence *both direct and deductive is needed to justify our conclusion* We should like to review this evidence now

a. Anatomical It can be shown that eccrine sweat duct pores are often so situated as to allow the eccrine sweat to flow down into the hair follicles As shown in Fig 28 the occasional eccrine duct lies in extreme proximity to the follicle orifice Others opening into the sides of small skin grooves which are directed into a hair follicle orifice can supply sweat which gravity will draw down into the follicle openings Using special anatomic dissection techniques we have further demonstrated the surface relationship between the hair follicle orifices and eccrine duct pores (Figs 29 30)

Application of a water repellent (silicone) to the axilla promotes eccrine sweat droplet formation and reduces free spreading of sweat in film form In subjects so treated with silicone it is not



Fig. 28 Eccrine duct opening near hair follicle Photomicrograph of section of axillary skin showing hair follicle with an apocrine duct emptying into one side of the follicle (on the left) In addition on the right an eccrine duct can be seen as it coils upward and opens quite close to the hair follicle orifice H and E Mag × 130

Fig. 29 Hair follicle with attached apocrine duct After immersion in 3% ammonium hydroxide a small piece of axillary skin was stripped of its epidermis The undersurface of the detached epidermis is shown above Two hair follicles are seen projecting downward from the epidermis An apocrine duct is seen emptying into one of these follicles On each side of the follicles is an eccrine duct the glandular portion of which was retained by the corium Mag × 27



Fig 30 Pore pattern in axilla Another specimen of axillary skin was immersed in 3% ammonium hydroxide for 3 hours and the stratum corneum stripped off Transillumination of this skin reveals the epidermal surface with large and small pores The larger pores are hair follicle openings some receiving small apocrine duct pores The small round light areas not associated with the hair follicles are eccrine duct orifices Note the proximity of many of these to hair follicle openings Mag × 9

possible to see any primary sweat droplets developing in response to heat

On other hairy areas of the skin in which no apocrine sweat glands are found, such as the leg or thigh, the hair follicles may also appear to be the sites of origin for eccrine sweat Here it is apparent that physical factors are responsible for this finding

b. Histological and Histochemical. A study of the apocrine secretory cells reveals the uniformity of character A single type *of secretory cell speaks for a single type of secretory product*

Histochemically it is significant to note that the axillary apocrine sweat gland in man possesses little or no glycogen in contrast with the well-known glycogen deposits of the eccrine sweat gland It is our belief that if the apocrine sweat gland were to produce an additional secretion which is eccrine-like not only in appearance



Fig 31 Methylene blue excretion in eccrine sweat After injection of 0 2 cc of 0 1% methylene blue solution into the axillary skin subsequent injection of 0 05 cc of pilocarpine (1 10 000) produced blue eccrine sweat droplets in this area Note prominent blue droplet in center of photograph Other blue droplets were also seen but are not evident in black and white photo Stimulation of apocrine sweating in this area produced only white apocrine sweat

but also physiologically it should show glycogen in at least some of the secretory cells

We have demonstrated that the apocrine sweat gland has adrenergic but no cholinergic nerves It is difficult to accept the view therefore that cholinergic stimuli affect this gland

c Physiological The physiological observations made also fully support our conclusion regarding the origin of the clear colorless fluid It always appears in response to measures which invariably stimulate the eccrine sweat gland The quantitative response and latent period correspond with those of eccrine sweating

Mixing of the two secretions was not observed when one secretion was made to appear immediately after the other This would certainly be expected if both were arising from the same gland

It has long been known that the injection of methylene blue into the skin will result in the coloring of eccrine sweat (Fig 31)

We have found that this does not occur in the apocrine sweat gland This differential dyeing technique was used to distinguish eccrine from apocrine sweating in the axilla After the injection of methylene blue, the subsequent injection of acetylcholine led to the production of a blue follicular fluid, while stimulation with epinephrine resulted in cloudy white secretion

d. Pharmacological: All of the drugs which result in the appearance of the clear, colorless, "follicular" fluid are specific for the production of eccrine sweat Moreover, atropine will block this response, just as it inhibits eccrine sweating

e. Chemical The colorless "follicular" fluid is chemically identical with eccrine sweat It is free of protein which sharply separates it from apocrine sweat In addition, its pH matches that of samples of known eccrine sweat from the same axillae

f Theoretical. From a speculative viewpoint, there is no necessity for the axillary apocrine sweat gland to serve in a thermoregulatory role, and it would be difficult to understand any apocrine gland response to heat The axilla abounds in eccrine sweat glands and normally an excessive quantity of eccrine sweat is provided

The proponents of the dual secretion theory have raised objections to our concept regarding the origin of the clear follicular fluid It has been stated that the apocrine sweat gland is capable of producing sweat in large volume This notion is based on the fact that the horse which possesses only apocrine type sweat glands secretes large volumes of clear sweat in response to thermal stimuli However as we noted earlier it is not at all certain that the sweat gland of this animal is truly apocrine functionally comparable with the apocrine gland in man Furthermore we do not feel it is possible to predict the function of a human gland on the basis of comparative physiologic studies in lower forms

It has also been cited that the apocrine gland is capable of producing an eccrinoid type of secretion in rather large volume because patients with congenital ectodermal defect have been shown in many instances to be completely anidrotic except in the axillae In these patients the axilla may present a relatively normal amount of sweat and it has been considered that all of this arises from the apocrine glands It is now known that this is not necessarily true We have verified the presence of well

developed eccrine, as well as apocrine sweat glands in the axillae of such patients and it is our belief that the eccrine glands present were responsible for the normal sweating seen in the axilla

In conclusion, we feel that the evidence is overwhelmingly in favor of the view that the human apocrine sweat gland produces a single type of secretion, the viscid, turbid white product The clear, aqueous secretion one may see at the follicle orifice is in reality, eccrine sweat

D APOCRINE SECRETION

1 Definition—General Features

Apocrine secretion is the designation we have employed to describe the formation of apocrine sweat in the secretory tubules It is to be regarded as a process separate and distinct from apocrine sweating the appearance of apocrine sweat on the skin surface Thus the apocrine sweat gland is much like the mammary gland, another apocrine gland, in which there are two such distinct functional phases The eccrine sweat gland, on the other hand, differs markedly for its secretion is not formed continuously or gradually but rather immediately, in response to some stimulu such as heat, emotion or a drug

A casual examination of the histologic appearance of the apo crine secretory cell would quickly lead one to believe that the decapitation phenomenon is in reality the mode of secretion operative in these glands However, some doubt has been raised regarding the veracity of this notion Montagna, examining frozen sections unaltered by tissue fixatives, has demonstrated the presence of a fine fringe at the luminal border of the secretory cells (Figs 9 19) This is seen only at the higher limits of magnification under the light microscope and not well with thick sections or fixed material Electron microscopy has recently been utilized to examine the human apocrine sweat gland and has confirmed the presence of this luminal 'fringe (109) Montagna believes that it may represent tiny droplets of apocrine sweat as they are being released from the cell

It was pointed out that the apocrine sweat gland tubular cells show marked variation ranging from the high columnar cell full of cytoplasmic granules to the low cuboidal or flat cells with a

minimum of cytoplasmic elements. Some cells are so flat as to appear atrophic and in some cases they probably are. As we shall point out later, it is not uncommon to find a segment of an apocrine tubule with atrophic secretory cells or perhaps an entire gland in this state. Usually luminal casts may also be seen in such tubules and we feel that most develop as a result of ductal obstructions above, following maceration or other injury to the stratum corneum.

The presence of pigment granules, probably lipofuscin, has been mentioned and will be discussed later under chromidrosis. These granules are responsible for the occasional color in apocrine sweat.

Intracellular vacuolation is not uncommon in the secretory cell of the apocrine sweat gland (Figs. 7, 32). The significance of this is not known, but it is apparently related to the secretory process. This vacuolar appearance is seen principally in the cells with higher, more columnar epithelium.

The absence or at best presence of only minimal amounts of glycogen in the apocrine secretory cells is indeed significant. Glycogen is an energy substance and is present in cells with a high rate of secretory activity. For example, the eccrine secretory cells contain abundant quantities of glycogen and after exhaustive eccrine sweating this glycogen is decreased or depleted from the gland. The eccrine gland is capable of producing great quantities of secretion also, up to one liter or more per hour under heat stress. The apocrine sweat gland's secretory cells, however, operate at a low rate forming a small quantity of secretion, entirely consistent with their glycogen content.

2 Effect of Natural Factors—Age, Sex, Race

The amount of apocrine sweat one sees on the skin surface is naturally a reflection of the amount of apocrine secretion that has proceeded below in the tubules. The amount of apocrine secretion in turn is dependent on the state of glandular activity and on the glandular size.

We have shown that *age* can affect apocrine sweating. This is primarily the result of the secretory state of the gland. In the child with no apocrine sweat there are few if any actively secreting cells. At puberty such secretion begins with the eventual peak of activity reached during adult sexual life. After the climacteric

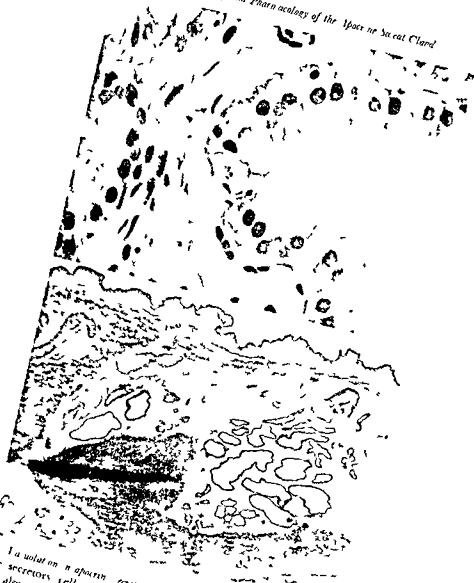


Fig. 32 Involution in apocrine secretory cell. Segment of apocrine tubule showing apocrine secretory cells. Note vacuolated appearance of many of the cells. Observe also cytoplasmic granules, pinched-off luminal tips of secretory cells and casts in lumen of tubule. H and E. Mag x 900

Fig. 33 Apocrine sweat gland in the elderly. Section of axillary skin from a healthy White man age [illegible]. Note small overall size of gland plus the dilated tubules lined by atrophic flat epithelium. H and E. Mag x 30

secretory function again wanes with consequent diminution in the *amount of apocrine sweat* It should be recalled however, that we have seen apocrine sweat in individuals even as old as 75 years However, as is apparent from a histological examination of the axillary skin of the aged (Fig 33), the apocrine glands are smaller and show considerably fewer active secretory cells with *high columnar epithelium*

The influence of *sex* on apocrine secretion is not marked The apocrine sweat glands of the adult female appear to be somewhat smaller than those of the male and show comparably smaller quantities of apocrine sweat

Profound differences in apocrine secretion may be seen as a result of *racial* variations The Negro has apocrine sweat glands which for the most part are significantly larger than those of the Caucasian (Fig 2) This, of course, results in greater quantities of apocrine sweat which appear on the skin surface In addition *chromidrosis of axillary glands is more common in the Negro* Indeed we have rarely observed axillary apocrine chromidrosis in white subjects although two of our patients with localized chromidrosis of the face were White It seems that the Negro apocrine sweat gland secretory cells function at a higher rate of activity also *They appear to have more activity* histologically and the refractory period for apocrine sweating in the Negro is generally shorter It is realized that the latter could easily reflect the greater size of the gland rather than an increased secretory rate

Schiefferdecker stated that the Australasians possessed the largest and most active apocrine sweat glands (6) We have not examined any individuals who would fall into this racial category However it is well-known that Orientals particularly the Japanese have little or no body odor as a general rule and this of course is a definite indication of apocrine sweat gland activity (8) We have examined several Japanese and Chinese men and have confirmed this to our satisfaction Nordic races were presumed by Schiefferdecker to have the smallest and least developed apocrine sweat glands

3. Effect of Endocrine States

The impact of *puberty* on *apocrine sweat gland function* is marked indeed as is also that of the climacteric In addition it

has been stated that other endocrine states will influence this gland

For example, numerous observers have described cyclic changes in the apocrine tubules which correspond with various periods of the *menstrual cycle* The majority feel the secretory activity is greatest premenstrually or during the menstrual flow (45, 46, 47) Others have stated that no correlation can be made relating to menstrual activity (48) Our experience would support this latter view, as does Montagna in his recent careful study (22) As this author points out, and we fully concur, the secretory cells may normally show such marked variation from gland to gland that it is difficult to assess the overall functional state of the gland Montagna found no histochemical alterations of note either While there may be changes occurring they are not detectable by present methods of study

Pregnancy has also been described as a period in which dramatic changes in apocrine secretory activity occur Again the literature contains conflicting reports on whether there is an increase or a decrease in glandular activity during pregnancy and there seems little point in detailing them here (49, 50, 51, 52) We have not noted a remarkable increase or decrease in the amount of apocrine sweat in the pregnant women we've studied, but would hasten to add that these women were not seen before their pregnancy nor studied for a long period after puerperium Interestingly, in the few women examined within the first week after delivery, at a time when the mammary gland is quite active, we were unable to detect a significant increase in apocrine sweat

It is significant to note that one subject examined seemed to show a diminished rate of growth of the axillary hair during pregnancy If hair growth is to be used as an index of appendageal (at least those appendages that are derived from the primary epithelial germ embryologically) activity, then perhaps some decreased apocrine functional activity did occur in this patient However, the apocrine response in this patient showed no appreciable change In addition, other women failed to show a comparable decrease in axillary hair growth

There is one bit of evidence, however, that suggests that apocrine secretory activity is diminished during pregnancy This is the fact that most patients with Fox-Fordyce disease improve

dramatically during pregnancy and that the disease recurs again after delivery While it is true other explanations may be offered for this improvement, we feel it may speak strongly in favor of decreased secretory activity during this period

The *climacteric* represents the era in which the apocrine sweat glands show the twilight of their functional activity We have examined elderly males for apocrine sweating as described in an earlier section In general the response was decreased in the elderly but we have seen some apocrine sweating in a subject 75 years of age Histologically, the retrogressive changes are quite apparent The glands are smaller in overall size, and there are fewer tubules showing active secretory activity There is an increased number of atrophic tubules also, with cellular casts in many of the tubular lumens (Fig 33) We have not had the opportunity to study histological specimens from the axillae of women of the post-climacteric era although Montagna has described changes similar to those outlined above in our male subjects However, we have examined the axillae of such women for the presence of apocrine sweat Similar results in eight women over 55 years of age as in the males referred to above were recorded The apocrine response was diminished in all, although the eldest woman observed 67 years of age, showed some definite apocrine sweat in her axillae

4 Effect of Systemic Disease

To our knowledge, involvement of the apocrine sweat gland by systemic disease processes has never been described We have not studied this problem specifically However we have seen normal axillary apocrine sweating in response to local epinephrine and to mental stimuli in one individual with sarcoidosis, in two with moderately advanced pulmonary tuberculosis one with leukemia, in one subject with diabetes mellitus, and in one man with hemochromatosis The latter did not show colored apocrine sweat interestingly It should be recalle[illegible] at the color in chromidrotic apocrine swe[illegible] has been attri[illegible] increased quantities of iron in the secr[illegible] nf [illegible] te [illegible] e unable to secure a biopsy of the [illegible] n t [illegible] check this point more carefully

It is quite possible that people with marked debilitating diseases resulting in cachexia and inanition or where there is prolonged agony may well show degenerative changes in the apocrine sweat gland. We have often noted that this gland shows autolysis relatively early post mortem and such changes may even begin before death in processes such as those referred to above.

5 Effect of Deodorants

In 1949, Sulzberger, Zak and Herrmann showed histologically in biopsy specimens from the axilla that aluminum chloride preparation produced a degenerative change in the apocrine tubular cell (53). They also recorded diminished eccrine sweating incidentally, presumably because of ductal occlusion resulting from periductal inflammatory changes. Our preliminary work suggested that aluminum chloride *paste* preparations might reduce or abolish apocrine sweating. Because of the importance of deodorants in our modern society, we decided to investigate this problem in some detail. Although greatest emphasis was placed on the aluminum preparations, we also studied the effect of the surface active agents and the newer zirconium salts and their effect on axillary sweating. We shall not describe our studies on the effect of deodorants on eccrine glandular activity in this section (cf Body Odor). Rather we should like to focus on the apocrine sweat gland. While our special interest in this chapter is related to *apocrine secretion* per se, we must use our observations on *apocrine sweating* responses in these subjects. Obviously an alteration in this latter activity could reflect a change in apocrine secretion.

Method and Materials

Ninety men were selected from approximately 160 subjects for a study of apocrine sweating. All of these men had abundant and symmetrically equal apocrine sweat responses. The axillae were unshaved and washing was limited to once daily. Nothing was applied other than the product under study. The following preparations were studied in 10 men each:

(a) 25% aluminum chloride in aqueous solution

(b) spray deodorant (commercial) containing aluminum chloride

(c) spray deodorant (commercial) containing an aluminum salt
(d) cream deodorant (commercial) containing an aluminum salt
(e) stick deodorant containing an aluminum salt
(f) stick deodorant containing a zirconium salt
(g) a cream deodorant containing a zirconium salt
(h) a cream deodorant containing a surfactant
(i) zinc oxide paste

In the case of the aluminum chloride solution, the application technique consisted of placing gauge pledgets (10 x 10 cms) saturated with the solution in the axilla for five minutes daily for seven days All other test substances were applied in one axilla for five minutes once a day for seven days In all instances, the opposite axilla served as a control and was untreated except for the usual washing At the end of a week, the axillae were carefully cleansed with 70% alcohol to remove all debris accumulated cream paste or liquid deodorant, so that there would be no difficulty in identification of apocrine sweat These men were then given a standard test dose of epinephrine (0 15 cc of 1 1000 solution) subcutaneously in each axilla Comparison of the response in treated and control sides was then made In addition in at least three men in each group biopsies of the treated and control axillae were taken for histologic study of the glands after such treatment These were fixed in formalin and stained with hematoxylin and eosin

Observations

In all subjects studied, there was no significant decrease in the quantity of apocrine sweat in the treated or untreated axillae In some of the men who had used the aluminum chloride preparations miliarial vesicles were produced on the treated areas

The zinc oxide was used to determine the possible mechanical blocking effect of such a thick preparation It too was ineffective which is not surprising since the glands will 'sweat' against an external pressure of 225 mm of mercury

Histologically we could find no degenerative atrophic or other change within the apocrine secretory cells, in the ducts or in the stratum corneum These as well as other structures observed were entirely normal and indistinguishable from the control skin Comment regarding the effect of these substances on odor reduc

tion in the axillae will be discussed later in the section on Body Odor It is concluded that none of the materials studied has any apocrine *antiperspirant* effect

6 Effect of Hormones

The natural history of the apocrine sweat glands in man indicates that they are under endocrine control The precise relationship of such hormonal control is not at all clear, however There is little experimental evidence which indicates that any hormonal principles can induce changes in apocrine activity Shelley and Cahn, in an exhaustive study using topical and systemic administration of adequate doses of various forms of estrogens, androgens, progesterone, thyroxine, the growth hormone of the pituitary, prolactin and chorionic gonadotrophin, alone, and in various combinations, found no appreciable alteration in apocrine sweating or in the histologic appearance of the apocrine sweat gland (54) These authors noted no changes in any of the other structures found in axillary skin as well

Hormonal effects on cutaneous structures which have been described in animals have not been satisfactorily reproduced in man probably because of species variations and dosage differences In man, significant changes have been seen in the skin only after long term high dosage hormonal therapy in clinical disease such as breast carcinoma (55) In such instances however histologic and control observations were usually lacking and the underlying disease process may have altered the observed tissues

Some of the prime difficulties in previous studies on human skin may have been lack of absorption relatively low dosage levels and short term trials In an effort to obviate these difficulties we decided to employ hormone containing pellets implanted subcutaneously in the study area as an experimental approach Because of the importance of androgens and estrogens in sexual development and because these substances have long been implicated for the changes in human skin believed to be induced endocrinologically it was decided to use these substances in this study Dosage varied from one to three pellets in the sites to be observed and they were left in place for periods varying from one to five months The hormone was intimately in contact with vessels appendages and other skin structures with this technique

TABLE 1

No of Subjects	Hormone(s) Used and Dosage	Biopsy After	Comments
1	Progynon – 25 mgm	1 month	
1	Progynon – 25 mgm	2 months	
1	Progynon – 25 mgm	3 months	
1	Progynon – 25 mgm	4 months	
5	Progynon 25 mgm	5 months	Two of these subjects developed bilateral gynecomastia and one subject developed unilateral gynecomastia on the treated side
1	Orcton – 75 mgm	1 month	
1	Orcton – 75 mgm	2 months	
1	Orcton – 75 mgm	3 months	
1	Orcton – 75 mgm	4 months	
4	Orcton 75 mgm	5 months	
2	Progynon – 75 mgm	3 months	Bilateral gynecomastia developed in both subjects
2	Orcton 150 mgm	3 months	
2	Orcton 225 mgm	1 month	
1	Orcton 225 mgm	3 months	
1	Orcton 150 mgm in one axilla vs Progynon 75 mgm in opposite axilla	3 months	Bilateral gynecomastia
2	Orcton 75 mgm in one axilla vs Progynon 75 mgm in opposite axilla	3 months	Bilateral gynecomastia developed in both subjects

Emphasis should be placed on the fact that in this study, the hormone-containing pellet was actually in contact with many of the structures of the skin (Fig 34) Using the implant technique, the local concentration of the hormone in the skin was far higher than that which could be achieved by any systemic or topical administration The failure of these large 'local' dosages of estrogen and androgen to produce change in the apocrine sweat gland and other skin structures, in the face of observable hormonal effects (gynecomastia) indicates that *elevation* of androgen and estrogen concentrations in the skin (of the adult male) were without effect, despite the fact that these very substances *may* be responsible for the continued activity and normal function of this skin and its appendages Furthermore, these findings support the view that neutralization of one hormone cannot be achieved by

the administration of another Certainly, the estrogen levels in the axillary skin of our subjects with progynon implants far exceeded the physiologic levels of androgen normally present

An obvious objection to these as well as previous studies of the effects of hormonal substances on human skin might concern the subject material used It may well be that one will be able to determine the controlling endocrine principle or principles only by studying pre-pubertal children We fully recognize this possibility Unfortunately, such subjects were not available to us at the time of these studies

In conclusion, we were unable to postulate the specific hormone or hormones which may regulate apocrine secretory activity, despite extensive investigation in this direction The recent work of Lorincz et al indicates that the activity of the sebaceous gland may be regulated by a specific trophic factor of the anterior pituitary (57) It may well be that the human apocrine sweat gland is similarly controlled by this same or another pituitary hormone

7 Effect of X-ray

The effect of X radiation on the cutaneous appendages has always attracted great interest because of the use of this modality in a variety of the dermatoses affecting these structures It is stated that a total of 1100 roentgens will depress the holocrine activity of the sebaceous gland A dosage of approximately 350 r will cause temporary epilation of scalp hair and over 600 r is required to produce permanent alopecia (58) It should be emphasized that other skin areas require different dosages for similar epilating effects The beard, for example, may only yield temporary and perhaps partial hair loss after 850 r It is recognized that this dosage is approaching that at which skin damage (radiation sequellae) may eventually develop

In contrast to holocrine function, however, the merocrine organ of the skin, the eccrine sweat gland, requires about 2200-2300 roentgens, it is believed, to cause inhibition of its secretion (58) This has not received experimental confirmation, however, and this figure may be quite inaccurate

No data are available regarding the amount of X radiation required to affect apocrine secretion Because it is thought of

as intermediate between the eccrine and sebaceous glands, it has been speculated that a dose of 1700-1900 roentgens might produce this effect. The problem of size of the gland and its greater depth must also be considered however, and perhaps would necessitate an increased quantity of irradiation It is noteworthy that we detected adequate quantities of apocrine sweat in the axillae of a young man who had received 1000 r of heavily filtered (0 5 mm Cu) X-ray 5 years earlier for eccrine hyperidrosis of the axillae The eccrine sweating was also not depressed, and axillary hair growth was as luxuriant as before It is probable that much of the X-radiation given in this case was actually received at a much deeper level than in the skin because of the great filtration employed In another subject, we administered 800 r (1 0 mm AL filter) in air at one sitting to a 5 0 cm area in the axilla The subject was observed at weekly intervals for one month then monthly for three additional months No apparent change in apocrine sweating was noted (his axillary odor was not decreased) nor was there any hair loss

In conclusion, it may be restated that the amount of X-radiation required to produce a significant decrease in apocrine secretory activity is unknown It is in excess of 800 roentgens and probably above 1000 roentgens

8. Relation to Pilo-sebaceous Activity

Because the apocrine sweat gland is a derivative of the same parent germ it was thought that the function of this gland might be related in some way to pilo-sebaceous activity However, no specific changes have been noted in any studies to date but such may be extremely subtle In some 'skin cycle' animals, such as the mouse and rat, parallel changes in the sebaceous glands, metabolic activity of the skin and other functions have been demonstrated (59 60) Since all of the hairs in these animals are in *the same stage of their cycle simultaneously* it is relatively easy to examine this problem In man however, as in some other animals, hairs do not reach anagen or telogen together — there is no synchronization of hair growth These animals are not "skin cycle" animals and no constant relationship between hair growth and other cutaneous activities has been demonstrated However, if "unit" appendageal function were considered, perhaps

some relationship between hair and associated glandular function could be appreciated After studying several axillary biopsies carefully with this in mind, we could come to no conclusion regarding the possible relationship of hair cycles and glandular activity Axillary hairs in anagen may have associated glands (whose ducts empty into that follicle) which are indistinguishable histologically from those whose related hairs are in telogen Similarly, after manually epilating several hairs in the axillae of 4 subjects and subsequently biopsying these areas at 2 and 4 week intervals, we could not influence apocrine glandular activity despite producing an abrupt change in the growth cycle of associated hair follicles It should be emphasized that serial sections, properly cut in the long axis of the hairs, were necessary for this study While there is every reason to believe that there might be a functional relationship between hair follicles and derivative apocrine sweat glands, we are as yet unable to demonstrate it

E DISCUSSION AND SUMMARY OF APOCRINE SWEAT GLAND PHYSIOLOGY

Probably the most decisive single piece of evidence provided by our studies of the physiology of the apocrine sweat gland was the observation that apocrine sweat could be made to appear by mere manual compression of the axillary skin This simple fact *proves at once the following*

1 That the actual secretion of apocrine sweat must be a process independent of that which causes its appearance on the skin surface This latter more dynamic phase of apocrine function we have chosen to designate apocrine sweating Apocrine secretion is in fact a slow more or less continuous activity much like the formation of milk in the mammary gland
2 That an expressive or contractile force which empties the tubules of preformed apocrine sweat, is responsible for apocrine sweating We subsequently identified this contractile force as the myoepithelium the smooth muscle layer which envelops the apocrine tubules All of the phenomena concerned with apocrine sweating are dependent upon activation or inhibition of the myoepithelium

Let us recapitulate the salient features characterizing the con-

trol of each of the functional phases of apocrine sweat gland physiology

Apocrine sweating is under the control of adrenergic fibres of the autonomic nervous system Neural control is operative because an instantaneous wide spread response is seen following the proper emotional and sensory stimuli Moreover, local anesthetics will block this response while local arrest of the circulation will not The adrenergic nature of the innervation is apparent since apocrine sweating may be produced by adrenergic and not by cholinergic drugs In addition, the absence of specific ChE about the apocrine sweat gland tubules indicates an absence of cholinergic nerves, thus confirming the observation that there is a single, adrenergic supply There are no inhibitory fibres to this gland

Apocrine sweating may also be produced by other local, somewhat artificial (unphysiologic?) stimuli Drugs, such as pitocin, which excite myoepithelial contraction, can induce a local response Physical stimuli, such as stroking or rubbing of the axillary skin may also activate the myoepithelium resulting in apocrine sweating It is conceivable that a similar stimulation may be effected in our daily lives by the rubbing of the axillary skin as produced by the swinging of the arms in walking or running This may well represent a normal means by which the apocrine glands are emptied periodically

The regulation of *apocrine secretion* is not perfectly understood as yet although the importance of the endocrine system cannot be overemphasized The influence of puberty, the climacteric and endocrine states such as pregnancy have been mentioned However despite extensive experimental investigation, the specific hormones which produce these alterations have not been identified We know of no systemic disease which effects apocrine glandular activity although the early development of autolysis post mortem suggests that degenerative changes may occur after prolonged cachectic illnesses None of the deodorant preparations presently available have any effect on apocrine secretory activity Indeed they have relatively little antiperspirant effect in the axilla They function mainly as deodorants The dosage of X-radiation required to depress axillary apocrine secretion is unknown It is certainly in excess of 1000 r

TABLE II

	Apocrine Sweat Gland	*Eccrine Sweat Gland*
1 Derived from	Primary epithelial germ like hair and sebaceous glands	Eccrine sweat gland germ
2 Secretory cells	Single type, variable height depending on stage of secretion Numerous granules no canaliculi	Two types Cell height constant Have inter and intracellular canaliculi no granules
3 Myoepithelium	Well developed Functional importance Contracts to produce apocrine sweating	Poorly developed Probably non functional Pressure generated from secretory activity forces eccrine sweat to surface
4 Character of Sweat	Turbid May be colored and may fluoresce	Clear watery
5 Localization in man	Restricted	Generalized
6 Localization in other mammals	Generalized	Very restricted or absent
7 Autonomic innervation	Adrenergic only	Cholinergic Adrenergic supply if present of no importance functionally
8 Begins to function	At puberty	At birth
9 Secretion of sweat	Slow gradual process resulting in storage of minute amounts equal to tubular volume Does not occur at time of apocrine sweating Under endocrine control	Very rapid process Great quantities can be formed up to one liter per hour Actual secretion takes place at time of sweating
10 Refractory period	Once gland is emptied for 24 72 hours	None seen after any physiologic stimulus Sweating continues as long as stimulus remains
11 Responds to	Emotional stimuli not to heat	Heat emotional stimuli
12 Physiologic importance	Little or none Atavistic scent gland Important primarily because of local disease	Vital in hot environments Major thermoregulatory organ

As a final note it is of value to contrast the mode of function and activity of the two varieties of sweat glands in man, the apocrine and the eccrine This is conveniently done in tabular form Anatomical and comparative features are included also since they provide a better understanding of the physiology of these glands It should be emphasized that eccrine secretion and eccrine sweating take place at the same time whereas apocrine sweating is a process independent of apocrine secretion

IV

THE NATURE OF APOCRINE SWEAT

A. PHYSICAL CHARACTERISTICS

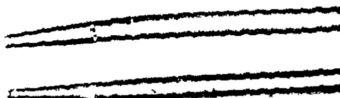
Apocrine sweat is a turbid fluid (Fig 35) It is this property of turbidity which is of great importance in the differentiation from eccrine sweat, a clear, watery secretion However, the cloudy nature of the apocrine sweat varies greatly from person to person In some, especially the Negro, it may be so thick as to resemble cream, while in others, in order to identify it with certainty, it is often necessary to collect some of the material in a small capillary tube for examination against a black background By so doing, one can readily distinguish apocrine sweat which always shows some turbidity, from clear, aqueous eccrine sweat It is worth noting that it may be difficult or impossible to even collect some of the very thick apocrine sweat in a capillary tube because of its viscosity It is apparent therefore that the specific gravity of apocrine sweat will vary from that close to water to that equivalent to milk or cream

Apocrine sweat may also show some color Most commonly, a yellowish tint can be perceived although green, blue and bluish-black sweat may be observed infrequently

Apocrine sweat, while odorless when it initially appears on the skin surface, develops a distinctive odor within a short time because of bacterial decomposition

If undiluted by eccrine sweat, apocrine sweat dries quickly to *appear as a glistening, glue-like cap resembling dried* varnish or plastic If collected in a tube, curd like particles will settle within the sweat as it ages (Fig 36)

Finally, whether dried or recently secreted, apocrine sweat may exhibit a true fluorescence when exposed to Wood light (Fig 20)



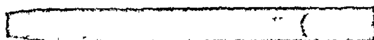


Fig 35 Apocrine sweat Two capillary tubes containing sweat are shown The upper tube contains clear *eccrine sweat* The lower tube contains turbid apocrine sweat

Fig 36 Curds in apocrine sweat Capillary tube containing apocrine sweat was allowed to stand for 24 hours Examination at this time revealed the development of curd-like aggregates (above) in the sweat

B CHEMICAL CHARACTERISTICS

The pH of apocrine sweat was measured using pHydrion Universal indicator paper with which 0 5 pH unit changes can be detected Samples of apocrine sweat were collected from twenty normal, healthy adult male subjects Both Negroes and Whites were studied and extremes of apocrine sweat ranging from the very turbid viscid variety to that close to eccrine sweat in appearance included Pure micro samples were collected in capillary tubes just after appearing at the axillary follicular orifices in response to epinephrine or emotional stimulation Pure samples of eccrine sweat were collected in similar tubes after emotional stimulation also

It was learned that the pH of axillary apocrine sweat ranged between 5 0 and 6 5 whereas the eccrine sweat readings were between pH 4 0 and 6 0 In a given individual, the apocrine sweat appeared to have a pH approximately 0 5 pH unit higher than the eccrine sweat but the differences were too slight to be of practical value in differentiation of the two secretions

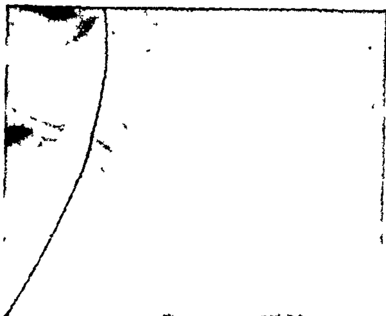


Fig 37 Iron in apocrine sweat on shirt A spot test (α α^1 dipyridyl) for iron was applied to the axillary section of a shirt stained with apocrine sweat The dark line in the right half of the photograph indicates the presence of iron It should be emphasized that this test is positive in only a small percentage of cases

The minute quantities of the apocrine sweat samples that could be secured necessitated the utilization of ultra-micro analytic techniques Spot tests proved to be the most satisfactory methods of determining the chemical composition (61) It was found that apocrine sweat in contrast to eccrine sweat, contains *protein* (using the 2 nitroso B-napthol test for tyrosine), *carbohydrate* (reducing sugars using silver nitrate), and *ammonia* (manganese nitrate silver nitrate) Although we were unable to demonstrate *lipids* by means of spot tests we feel certain of the presence of these compounds from the histochemical studies The spot tests for lipids are relatively insensitive procedures In addition *iron* in the form of *ferric iron* (α α^1 dipyridyl after reduction) is present in apocrine sweat although in no great quantities A positive spot test on the axillary section of a white shirt is shown in fig 37 Note the dark line indicating the presence of iron Apparently, migration of the iron was greatest producing this location for the

iron deposit in the moistened shirt. These results were quite irregular however, and in most people negative "shirt" tests were noted. Samples of apocrine sweat collected in capillary tubes gave a similar pattern on filter paper provided enough apocrine sweat was used.

We have not studied the chemical characteristics of apocrine sweat in other races, in women, after dietary restrictions or indiscretions, in areas other than the axilla or in patients with systemic disease.

C. BACTERIOLOGY

The axilla is a moist intertriginous skin site and as such harbors a maximal number of resident and transient skin micro organisms.

We attempted to outline the normal range of the bacterial flora found in the human axilla. Swabs were taken from the axillae of twenty healthy men and were inoculated on blood (horse) infusion agar. In general, the following bacteria were found routinely:

(1) Micrococcus pyogenes, var. aureus (coagulase-positive Staphylococcus), (2) Micrococcus pyogenes, var. albus (congulase-negative Staphylococcus), (3) Corynebacteria, (4) Aerobacter aerogenes, (5) Sarcina lutea.

Strauss and Kligman, in a later study of the axillae of twenty-nine healthy male subjects, found essentially the same organisms along with an occasional E. coli and Proteus vulgaris as additional transient organisms (57).

Little was known, however, regarding the bacteriologic state of apocrine sweat. Because of the possible importance of bacteria in the production of axillary odor, we felt it imperative to determine what organisms, if any, might normally reside in apocrine sweat itself. This information would be equally cogent in a consideration of the etiology of diseases of the apocrine sweat gland.

Method and Materials

Twenty healthy adult male volunteers with no abnormalities of the axillae were used as subjects.

The axillae were prepared in the following manner. The evening before the collection of the specimens, the axillae were closely shaved and cleaned carefully with Ivory soap. Again in the A.M. on arising, the axillae were cleansed with Ivory soap

Three hours later immediately prior to collection of the sweat samples the axillae were cleansed a third time with Ivory soap After rinsing the axillae were swabbed with a pad soaked in 70% ethyl alcohol Finally a 10 x 10 cm Steri pad saturated with 70% ethyl alcohol was applied to the axilla and left in place for 5 minutes

Collection of sweat samples Upon removal of the alcohol saturated Steri pad a thin film of alcohol was seen on the surface 1 1000 epinephrine injected subcutaneously to induce apocrine sweating Eccrine sweating was not observed in these subjects during this collection period

As soon as the apocrine sweat appeared it was collected in a sterile capillary tipped glass pipette approximately 20 cm in length The dilated distal portion of the collecting tube was plugged with cotton to insure sterility The narrow capillary end of the tube was then dipped in a tube containing sterile petrolatum thus sealing this end of the collecting tube to avoid contamination and evaporation of the specimen The entire collecting tube was then placed in a large sterile glass tube capped with cotton and promptly transported to the laboratory for bacteriologic study

Bacteriologic Techniques

The contents of the axillary tubes were placed in 1 cc of brain heart infusion broth Cultures were incubated aerobically and anaerobically Hanging drop and Gram stain preparations were made of the broth cultures and subcultures made to nutrient agar and blood (horse) agar When Gram negative bacilli were present in the cultures subcultures were also made to eosin methylene blue agar and S S agar The Brewer jar method was employed in the anaerobic studies Micro aerophilic conditions were established with this method also but the method modified in that hydrogen was added and the jar not completely exhausted of oxygen

Results

The bacteriologic studies of apocrine sweat showed the following

	Aerobic	*Anaerobic*	*Microaerophilic*
No of specimens	24	5	5
No with bacterial growth	4	0	0

Of the four specimens which showed bacterial growth, two contained organisms of the genus Corynebacterium, one of the genus Aerobacter and one of the genus Sarcina The first are normal resident organisms of the skin surface while the latter two may be found in the transient flora of the skin surface We feel that their presence in the four specimens was the result of accidental contamination of the apocrine sweat during collection It is of interest that no anaerobes were found in apocrine sweat since sebum has been shown to contain such organisms (Propionbacterium)

On the basis of the above described studies, we concluded that human apocrine sweat is normally a sterile fluid on its appearance on the skin surface

D BODY ODOR

Because of the purported significance of the apocrine sweat in the production of body odor, we undertook to study this problem in detail In studying the physiology of the apocrine sweat gland, we were impressed by the lack of appreciable odor in pure apocrine sweat as it initially appears on the skin surface Moreover, it was noted that after standing, such sweat later developed a definite foul odor which increased in intensity as time progressed In this investigation, we were particularly interested in the possible roles of bacteria, apocrine sweat and deodorants in the production of axillary odor (61)

Our preliminary studies indicated that apocrine sweat was sterile and odorless when it initially appeared on the skin surface

(1) We then proceeded to study *axillary apocrine odor in vitro* and to determine the role of the axillary bacterial flora in the production of this odor

Method and Materials

Ten healthy Negro men were chosen for this study No abnormalities were present in their axillae

Preparation of the axillae One axilla was prepared exactly as described above under Bacteriology of Apocrine Sweat The opposite axilla was unshaved and was not cleansed for at least 24 hours prior to collection

Collection of the specimens Collection of the specimens was identical with that described under bacteriologic study

Ten microtubes (Tubes No 1) were filled with pure apocrine sweat taken from the cleansed axilla, and 10 tubes (Tubes No 3) were filled with pure apocrine sweat taken from the uncleansed axilla In addition, another series of tubes (Tubes No 2), especially prepared with a thin film of hexachlorophene in absolute alcohol lining the interior of the tube, were filled with pure apocrine sweat collected from the uncleansed axilla All of these tubes were then allowed to incubate at room temperature and studied at varying intervals Several similar specimens were kept refrigerated at 0° C

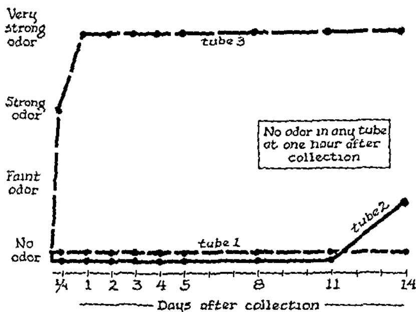
Examination of the specimens The specimens incubated at room temperature were then examined for odor in a careful consistent manner at 1 hour, 6 hours and 24 hours, then once daily up to the fifth day Later examinations were made on the 8th, 11th and 14th days They were read in the same order at each examination, i e, Tubes No 1 (containing pure apocrine sweat from the prepared axilla) Tubes No 2 (containing pure apocrine sweat from the unprepared axilla with hexachlorophene lining the interior of the tube) Tubes No 3 (containing pure apocrine sweat from the unprepared axilla)

The tube was broken at the capillary end and then tested for odor by two examiners, and the results were recorded independently by each examiner without knowledge of the other s reading

Results and Discussion

No odor could be detected in any of the tubes at one hour after collection, as illustrated in Graph I In tubes No 1 no odor developed throughout the entire 14 day period Tubes No 2 had no perceptible odor until the final reading on the 14th day, when a faint odor was recorded Tubes No 3 at 6 hours generated a strong odor which became very strong at 24 hours and remained at this intensity throughout the rest of the readings In the refrigerated specimens no odor ever developed

Of great significance was the fact that the odor developed in these tubes was, as far as we could tell, identical with that which we identify with the axilla of man It is not surprising that the refrigerated samples failed to develop any odor since the necessary bacterial activity would be absent under such conditions



GRAPH I

In summary axillary odor was reproduced in the "test tube" It developed within six hours after collection of pure apocrine sweat from an uncleansed, unshaved axilla No odor was noted in samples of pure apocrine sweat collected from the "sterile" axilla even after 14 days The addition of hexachlorophene prevented any odor from developing until the 14th day, when a faint yet typical axillary odor was recorded

It was concluded that bacterial action is necessary for the production of odor from apocrine sweat This experimentally reproduced odor was indistinguishable from the classical axillary odor seen in man

(2) An *in vivo study of axillary odor* was then devised in order to test the afore mentioned principle (in vitro) that bacterial action upon apocrine sweat would result in the typical body odor and that such odor could be prevented or diminished by inhibition of bacterial activity in the axilla A popular germicidal detergent pHisoHex® was used as the antibacterial agent in the study

Methods and Materials

Twenty-five healthy Negro men were chosen for this study and were divided into two groups of 10 (Group I) and 15 (Group II) men each. No abnormalities were present in their axillae, and axillary hair growth was good in all subjects.

Group I. Preparation of the axillae. No shaving of axillary hair was done in these subjects. One axilla was carefully washed for five minutes with phisohex once daily for seven days. The opposite axilla was also carefully washed for five minutes with pHisoderm® once daily for seven days. Thorough rinsing of the axilla with tap water was done in each case following each wash, but no other soap, deodorant, or alcohol was applied to these areas during this trial period.

Examination of the axillae. These men were tested for the presence of axillary odor at 1, 2, 8, and 18 hour periods. Subjects were placed in a supine position with their hands beneath their head and elbows directed laterally. Two examiners, unaware of what the previous treatment had been, carefully appraised these axillae for odor, each independently stating their findings to a recorder. A rest period of 10 minutes between readings was provided. Observations were recorded as negative (absence of odor) or positive (presence of odor) and no attempt was made to grade the readings. The odor of hexachlorophene which was in itself pleasant, very faint, and easily distinguished from the classic axillary odor, was recorded as negative (no odor), unless in axillary odor co-existed, in which case a positive reading was made. Differences in readings, when they occurred, were recorded as positive.

Group II. Preparation of the axillae. The axillary hair was unshaved in these men also. For three days a daily five-minute wash with pHisoHex (to one axilla) and pHisoderm (to the opposite axilla) was done. Thorough rinsing of the axillae with tap water followed the washing, and no other soap, deodorant, or alcohol was applied to the areas during this trial period.

Collection of specimens. Two and one-half hours after the last axillary wash, 10 of these men were seen and placed in a supine position with their hands beneath their heads and elbows directed laterally. With sterile scissors and forceps, axillary hairs were removed from the respective axillae and placed on blood agar plates. Only one hair was placed on each plate. They were then incubated at 37.5° C. for 48 hours.

In the other five men, axillary hairs were removed and cultured in the same manner 20 hours after the last axillary wash.



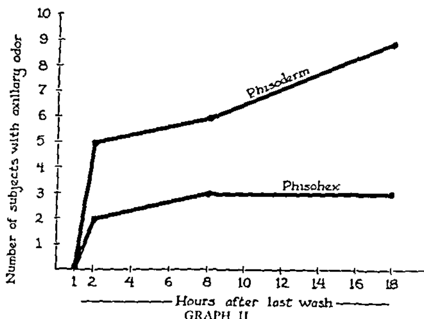


Fig. 38. Antibacterial effect of pHisoHex in axilla. Hair from pHisoHex washed axilla showing absence of bacterial growth on blood agar is illustrated in above photograph. Compare with hair below from pHisoderm washed axilla showing heavy bacterial growth. See text page 87.

Results and Discussion

Group I. As the graph II pg. 88 indicates, the pHisoHex-treated axillae showed a significantly greater odor protection than did the control pHisoderm treated axillae.

Group II. Of the hairs collected two and one-half hours after the last wash, none from the pHisoHex-washed side showed



GRAPH II

growth whereas all of the hairs from the pHisoderm-washed axilla showed luxuriant growth (Fig 38)

In the test 20 hours after the last wash, only one of five axillary hairs from the pHisoHex-washed axillae showed bacterial growth, while four of five pHisoderm-washed axillary hairs showed excellent growth after incubation at 37 5° for 48 hours

It has been shown that pHisoHex greatly reduces skin flora when used exclusively and repeatedly for cleansing The effect of the hexachlorophene was revealed by using the same detergent base, pHisoderm, as a control

This abolition of odor in the axillae of subjects using pHisoHex along with the concomitant axillary reduction in bacterial flora provides in vivo evidence that bacterial action is necessary for the production of body odor from the axilla

(3) The role of the *apocrine sweat* was yet to be elucidated It should be stressed that the secretion examined in the bacteriologic and odor studies thus far was not mixed axillary secretion but apocrine sweat alone The sweat droplets were collected at their points of origin immediately after their appearance No other secretion or at least only negligible quantities was included

Further proof of the importance of apocrine sweat is the fact that the appearance of the axillary odor can be correlated with the development of the apocrine sweat gland Thus, in the child before puberty, axillary odor is absent It is also diminished in the post climacteric epoch as activity of the apocrine sweat gland wanes

We studied five healthy adult males, ranging in age from 65 to 70 years for apocrine sweating and axillary odor It was found that four of the five had the usual axillary odor while the fifth, a 69 year old white man, did not show the typical axillary odor, but rather a flat, somewhat vague scent This patient also produced no apocrine sweat after stimulation with epinephrine

We concluded that apocrine sweat is the necessary substrate for the production of the classic axillary odor in man

(4) Other factors, notably *axillary hair* and *eccrine sweat* may also influence the development of the axillary odor

It is felt that the terminal hair of the axillary increases axillary odor production since it acts as a collecting site for apocrine sweat and debris and because it makes cleansing of the area more difficult Moreover, bacteria may cling to such hair We proceeded to investigate the role of hair in the development of the axillary odor

Method and Materials

Ten healthy Negro men were chosen for study No abnormalities of the axillae were present

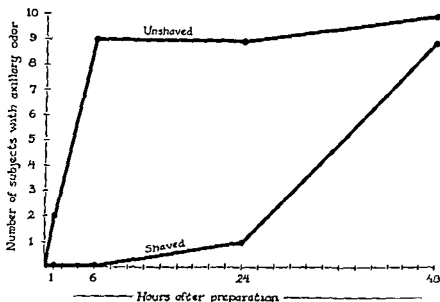
Preparation of the axillae One axilla was shaved and carefully washed with Ivory soap for 10 minutes The opposite axilla was unshaved and was also washed with Ivory soap for 10 minutes Each axilla was thoroughly rinsed with water

Examination of the axillae Olfactometric observations were then made in the same manner as previously described

Result and Discussion

The results are clearly illustrated in Graph III

The unshaved axillae of two men had a definite odor at the one hour reading, and at 6 hours 9 of these subjects showed such odor At 48 hours, all 10 of the group had the usual axillary



GRAPH III

scent Contrast these with the shaved axillae where no odor could be detected at 6 hours and at 24 hours only one man showed the usual odor At 48 hours, however, most of the shaved axillae developed odor

These findings substantiate the concept that retention of axillary secretion and bacteria will prompt an increase in odor The effect of shaving was quite remarkable, and it is understandable therefore, *that in women who shave their axillae regularly*, there is a markedly reduced axillary odor

Eccrine sweat is regarded as a sterile odorless fluid upon secretion, but it has been said that it develops an odor after standing for several hours, presumably because of bacterial action (64) However, this conclusion was reached after studies in which collection techniques were such as to allow for contamination of the specimens with keratin scales, debris, etc The necessity for the study of pure normal eccrine secretion in any investigation of its odor-producing capacity should be obvious *In our study* therefore, appropriate techniques were employed *to permit collection of uncontaminated eccrine sweat*

Method and Materials

Profuse thermal sweating was induced in a normal healthy man in whom the axillae had been thoroughly cleansed and shaved. Uncontaminated eccrine sweat droplets were collected from the axillae in the small glass pipettes in the manner described earlier. It should be stressed that the secretion was absolutely clear and watery in consistency.

Two sets of five tubes each were collected, viz., Tubes A, containing pure eccrine sweat, Tubes B, containing pure eccrine sweat and with a thin film of hexachlorophene lining the interior of the tubes.

In addition, small vials of contaminated eccrine sweat were collected from the trunk, legs, and neck. A "scraping" technique, that is, running the mouth of the vial along the skin of these sites, was used. The fluid in these vials was not clear, but was turbid white in appearance. These tubes were then incubated and were examined for odor at 2, 24, 48, 72, and 96 hours by two investigators independently.

Results and Discussion

It was found that no odor whatsoever developed in any of the tubes of pure eccrine sweat that were collected from the axillae.

Appraisal of the small vials containing contaminated eccrine sweat from the trunk, legs and neck revealed that a distinct odor was present at 48 hours. This odor was not pungent or at all offensive and was markedly different from the 'axillary odor' previously developed in vitro. This odor increased slightly in intensity at the end of 96 hours. These specimens were cultured for bacteria, and all showed definite heavy growth both in brain-heart infusion broth and on blood agar plates in 48 hours.

It seems apparent that eccrine sweat is of no importance as a primary odor source. It is practically all water thus providing an entirely inadequate substrate for bacterial activity. Such contaminants in improperly collected sweat as sebum, keratin, and debris could be responsible for some odor in eccrine sweat. However, unless apocrine sweat is also present, the odor generated in samples of contaminated eccrine sweat is, as shown above, *not* the typical axillary odor. Eccrine sweat in the axilla may provide an added impetus to bacterial growth, however, and in addition

aid in the volatilization of the odoriferous products of bacterial decomposition Thus the apparent "flush" of odor at an emotional crisis, when emotional eccrine sweating occurs Fresh apocrine sweat, while odorless when it initially appears on the skin surface, could also aid in the volatilization process

(5) Any investigation of axillary odor leads inevitably to a study of the effects of *antiperspirant-deodorant preparations* In an earlier section of this monograph, we demonstrated that *none* of the available products used today produces a significant reduction in apocrine sweating Furthermore, we were unable to detect any changes in the histology of the apocrine sweat glands, as had been reported earlier, and thus concluded that there was no impairment *in axillary secretory activity following the use of such preparations*

In these subjects, we also studied the effects of such preparations (see page 67) on axillary eccrine sweating The Randall starch paper-iodine technique was used as an indicator and representative prints are shown in Figure 39 It is apparent that no significant decrease in the amount of eccrine sweating was observed It should be stressed that these post-treatment prints were compared with similar ones taken before the application of the deodorant and revealed no differences in eccrine sweating It is probable that the eccrine sweat of the axilla washes away the aluminum salts and thus prevents the usual effects of these substances elsewhere viz, keratin damage and poral occlusion

While it has been shown that the aluminum preparations as commonly used in the axilla possess no remarkable antiperspirant activity it is possible that they may act as deodorants We confirmed this suspicion during the studies described above on the effect of antiperspirant-deodorant preparations on apocrine sweating Examination of the axillae of these subjects for axillary odor revealed a significant reduction in odor in about 60% (12 of 20) of the men studied as compared with normal odor production on the control side Even at 18 hours 3 of the men still showed absence of axillary odor while the others had developed such odor in the interim

It was concluded that these aluminum preparations (and zirconium products also) apparently act as deodorants in abolition of axillary odor



Fig 39 Lack of antiperspirant effect in axilla after aluminum Imprints (Randall technique) of axillary skin showing amount of eccrine sweating one week after daily applications of aluminum chloride solution to the *right* axilla and distilled water to the left Observe the lack of antiperspirant effect on the aluminum treated side

(6) The final phase of this part of our investigative program was concerned with the *mechanism of action* of the deodorant preparations containing aluminum salts now that we were convinced of their efficacy as axillary deodorants It was felt that the action might be antibacterial and or chemical in nature The following studies were done to explore these possibilities

Methods and Materials

Ten healthy men were again chosen for study The axillae were unshaved and were cleansed daily as usual On one axilla a saturated pledget of 25% aqueous aluminum chloride solution was applied daily for five minutes for three days A similar application of water was used on the control axilla Two and one half hours after the last application the men were examined and

axillary hairs were selected from the axillae and placed on blood agar plates. These hairs were collected with scissors and forceps which were kept sterile at all times. One hair was placed on each culture plate. The cultures were then incubated at 37.5 C for 18 hours.

Pooled apocrine sweat was then collected from 20 normal healthy men and placed in a small vial. At the end of 48 hours a very strong odor developed in this vial. One-tenth cubic centimeter aliquots of this apocrine sweat were then added to 3 cc of distilled water and to a 25% aqueous aluminum chloride solution respectively. The specimens were then examined immediately for any odor change.

Results and Discussion

Of the aluminum-chloride-treated axillary hairs from the 10 subjects, six showed no bacterial growth on the agar plates, four showed good growth. The axillary hairs of the control side all showed luxuriant bacterial growth at 48 hours. An example is illustrated in Figure 40.

The specimen containing water plus apocrine sweat gave the typical acrid odor one might expect. However, an instantaneous odor change occurred in the solution containing the aluminum chloride and apocrine sweat. The resultant odor was decidedly different from the original one and may be described as a somewhat sharp yet relatively inoffensive scent. Dilution of this solution of the apocrine sweat and aluminum chloride resulted in a gradual diminution of the odor to the point where it became pleasant. A similar odor was occasionally noted in the axillae of men treated with aluminum chloride in the previous experiment.

The antibacterial effect of aluminum is well known. However, it is apparently not as marked an effect as is that of hexachlorophene. It is our impression that the major deodorant effect of the aluminum preparations is antibacterial in nature, although in addition there appears to be a chemical action thus rendering the normal odoriferous products of bacterial decomposition inoffensive.

Speculation upon the relative effects of the various bacteria is interesting. We concluded that almost any of the organisms of the axillary flora was capable of producing this odor. It is possible,



Fig 40 Antibacterial effect of aluminum in axilla Hair from aluminum treated axilla (upper) showing absence of bacterial growth can be compared with hair from control axilla treated with distilled water showing heavy bacterial growth

of course that individual variations in axillary odor reflect either chemical differences in apocrine sweat or differences in resident bacteriologic flora or both Strauss and Kligman, confirmed our conclusion that any of the organisms found in the axilla could produce axillary odor They found that a wide diversity of species of bacteria could produce the axillary odor from apocrine sweat Both Gram negative and Gram positive organisms were represented (63)

Furthermore Ikai was able to eliminate axillary odor using a powder containing a mixture of anion cation exchange resins He

TABLE IV

HISTOCHEMICAL STUDIES OF PIGMENTED GRANULES OF NORMAL AND CHROMHIDROTIC APOCRINE SWEAT GLANDS (FORMALIN FIXED SPECIMENS)

	Subj No	*Biopsy Site*	*Granules*	*Fluorescence*	*Lipofuscin Stain (Schmorl Reaction)*	*Lipofuscin Stain (Hueck Stain)*	*Ceroid (Pearse)*	*Iron (Perls)*
	Clinical Case							
Chromidrotic	1	Face	++++	Yellow	++++	++++	+	0
	7	Axilla	++++	Yellow	++++	++++	0	+
	8	Axilla	+++	Yellow	+++	+++	0	++
	11	Axilla	++++	Yellow	++++	++++	+	++
Normal	1	Axilla	+	Yellow	+	+	0	++
	2	Axilla	+	Yellow	+	+	0	++

Paper chromatography revealed that the fluorochrome and the pigment had the same migratory pattern The question of solubility of the pigment was explored Dried colored sweat was insoluble in water but did disintegrate in 70% ethyl alcohol Although initially it was felt the pigment dissolved, observation under the microscope revealed that the pigment particles remained discrete and did not go into solution Furthermore the pigments proved to be insoluble in carbon disulfide, chloroform, carbon tetrachloride and pyridine

The initial pH of the colored sweat was approximately 6 0 Alterations of the pH of blue sweat had no effect on the color

Upon the addition of a crystal of the strong reducing agent sodium hydrosulfite, blue sweat became decolorized

Normal white apocrine sweat became yellow-brown on standing for several weeks A crude nonspecific test for carotenoids was positive — addition of sulfuric acid to a drop of yellow sweat on filter paper produced delicate strands of reddish material later becoming a diffuse violet The Carr-Price antimony reaction for vitamin A was negative

Bacterial cultures of colored sweat taken under sterile conditions were negative

The histologic data obtained from biopsies of three of these subjects, case No 1 (to be described on page 106) and normals can be summarized in Table IV

Clinical Studies

Because of the preponderance of apocrine sweat glands in the axilla, this site looms as the prime area in which apocrine chromid

rosis can occur The fact remains however, that the great majority of clinical cases of localized chromidrosis are in areas not thought to contain apocrine glands Localized chromidrosis has been described most frequently on the face, an area generally regarded as devoid of apocrine sweat glands We were fortunate to have referred to us for diagnosis, two cases of true, localized chromidrosis of the face Each was from the same city, curiously, and both proved to have colored sweat of apocrine sweat gland origin This was evident from the pharmacologic and physiologic studies and was confirmed by biopsy of the involved area in Case No 1

Case No 1 This healthy 29 year old unmarried white woman from Wilmington, Del first noted the appearance of "black sweat" on her cheeks when she was 19 years of age The fluid would appear at times of excitement, tension, or overheating and was immediately preceded by an aura of warmth in the involved areas The fluid dried to form a very dark flake or scale which was adherent to the skin The process was worse in the summer and showed short unexplained remissions from time to time Its appearance or severity had no relationship to diet, menses, or general health Her menarche had been at age 15 and a 6 month period of amenorrhea preceded the onset of the chromidrosis Sweating elsewhere was normal Other physicians had been consulted over this condition and all forms of topical therapy proved unsuccessful All cosmetics had been avoided for two years without effect A general physical examination revealed no abnormalities Her skin was normal except for a few pitted acne scars on the face After five to ten minutes in a thermal chamber, tiny, black- and brown puncta and droplets appeared on both cheeks Before drying the droplets could be wiped away readily However, if undisturbed and in the absence of eccrine sweat, they dried rapidly forming an adherent shiny-black, grayish-black, blue-black or brown flaky material (Fig 41) Many of these appeared to be in the sebaceous orifices At ordinary room temperature an injection of 0 10 cc of 1 1 000 epinephrine solution (commercial) in the left cheek produced about 25 droplets Many of these were black but some were white blue and green An injection of 0 1 cc of 1 100 pilocarpine nitrate solution in the right cheek gave a normal colorless eccrine gland response At a later date the local injection of 0 1 cc of 1 1000 atropine sulfate solution had no effect and failed to prevent the appearance of colored

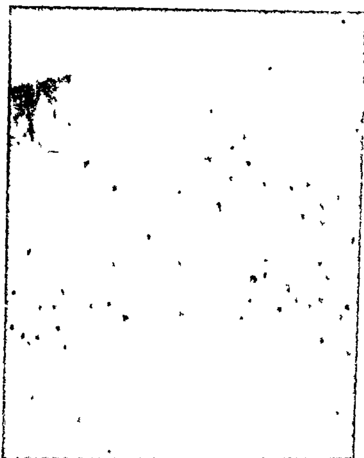


Fig. 41. Chromidrosis of face. Case 1. Note tiny dark droplets of chromidrotic apocrine sweat on cheek.

sweat in response to epinephrine. Finally, it was found that the colored fluid could be expressed manually. The lighter colored sweat showed a yellow fluorescence under Wood light (Fig. 42), whereas the black fluid and scale showed minimal or no fluorescence. Study of apocrine sweating in the axilla revealed it to be normal and of the common white variety. The cerumen also showed the normal yellow brown color. Five day patch tests with five of the patient's cosmetics were negative and subsequent eccrine sweating in the area was colorless. Her urine was normal in color and nonfluorescent. It remained unchanged upon



Fig. 32. *Colored sweat on cheek under higher magnification.* Two droplets of colored apocrine sweat from the cheek of Case 1. Note their follicular location. In the lower photograph observe the fluorescence of these same droplets on exposure to Wood light.



Fig 43 Histology of chromhidrotic glands Case 1 Biopsy of face of Case 1 with *facial chromidrosis revealed the presence of apocrine sweat glands as shown* above H and E Mag x 250

standing at room temperature Specimens of the colored fluid collected under sterile precautions revealed no bacterial growth The dried scales were insoluble in water but disintegrated in ether and alcohol However the pigment itself did not appear to be truly soluble in these solvents Local treatment with ion exchange powders and hydrogen peroxide was without effect

With local procaine (4%) anesthesia a small biopsy was secured from the left cheek On gross examination four small dark areas could be seen on routine sectioning and staining These corresponded to the size and location of apocrine glands In hematoxylin and eosin stained sections these apocrine as well as eccrine gland could be seen (Fig 43) The apocrine glands were small The tubular secretory cells appeared more basophilic than normal and showed numerous yellow brown granules of varying size and cellular location Moreover unstained histologic sections revealed these same yellow and brown pigment granules (Fig 44) Fluorescent microscopy demonstrated that the granules were autofluorescent (Fig 45) Myoepithelium could be seen about the apocrine gland Special stains for lipofuscin (Schmorl Hueck) (13) revealed positively staining



Fig 44 Pigment granules in chromidrotic apocrine gland Case 1 An unstained section of the facial biopsy from Case 1 shows increased numbers of pigment granules (compare with normal gland Fig 11) Mag × 2000

Fig 45 Fluorescence of pigment granules in chromidrotic glands Same section as Figure 44 after exposure to U V L (4200 A°) Note fluorescence of some of the pigment granules Compare with Figure 11 Mag × 2000



Fig. 46. Normal and chromidrotic (Case 1) apocrine glands Schmorl stain. Segment of secretory tubule of chromidrotic apocrine gland (upper) showing abundance of dark-staining Schmorl-positive (lipofuscin) material is to be contrasted with tubule from normal after same stain. Mag. x 2000

granular material in the apocrine tubular cell cytoplasm (Fig. 46). The Hueck stain for melanin was negative. The Pearse stain (19) for demonstrating acid-fast lipofuscins (ceroid) was weakly



Fig. 47 Chromidrosis of face Case 2 Photograph of cheek of Case 2 showing dried droplets of colored sweat These were made to appear by local injection of 0.05 cc pitocin

positive Perls ferricyanide stain for iron was negative (Table IV) On the basis of these clinical histologic and physiologic observations it was concluded that the patient had typical chromidrosis and that the colored sweat was arising from aberrantly placed apocrine sweat glands Dietary restriction of carotenoids failed to result in improvement of the condition in this woman

Case 3 This 26 year old unmarried white male was first seen by us at Fort Knox Ky while a U S Army corporal He was in good general health was blond and fair skinned He was born in Baltimore, Md but had spent his recent years in Wil

mington, Del, and lived there before induction in the Army He had not noted any abatement in the amount of colored sweat seen during the year while in the Army in Kentucky He stated that for about three years (age 23) he noticed blue-black "smoky" droplets on the malar areas of both cheeks (Fig 47) These were not seen before this age, during puberty or adolescence, and his development during these periods was normal in every respect He first noted these black droplets after taking a hot shower and they have generally been noticed since (1) after a hot shower, (2) after shaving (wet shave), (3) before getting ready for a date, (4) after emotional disturbances He has observed also that the colored secretion could be easily expressed manually He used to "squeeze" these skin areas about once a week to try to empty the glands Although he could not empty every gland, he would be essentially free of such exudation for about 6-7 days following such an expression No aura of warmth was recalled preceding the appearance of the colored sweat There was no apparent cycling or seasonal variation concerned with this secretion He did not tan easily usually developing a good erythema upon exposure to sunlight He noted no change in the chromidrosis after such exposures No colored secretion has been noticed elsewhere in the body and none in other apocrine areas such as the axilla or pubis His urine showed no changes in color initially or on standing Although he was a consumer of moderately large quantities of carotenoids in his daily diet, restriction of these foods failed to produce significant change in the chromidrosis

Examination of the skin of the face revealed a definite dusky pigmentation over the malar eminences This was slight but distinctly present and appeared to be deep within the skin Stroking of the skin of the face did not prompt a response Manual expression of the colored sweat was readily accomplished however The injection of 0 15 cc of 1 1000 epinephrine solution produced a beautiful response as did 0 1 cc of pitocin at a later examination Atropine failed to inhibit either response and procain did not block the responses to local injection of these drugs Pilocarpine (0 1 cc 1 10 000 solution) did not stimulate the appearance of the colored sweat Examination of the axilla for apocrine sweating after epinephrine and pitocin revealed an absence of colored sweat although the usual white apocrine product was evident The colored secretion was extremely minute in amount so small that it was difficult to even collect a representative sample in

a capillary tube Moreover, it dried very quickly forming the typical shiny cap over the orifice, almost always follicular Water and alcohol (with greater use) would remove the dried cap of colored material There was no fluorescence of any of this dark blue black sweat to Wood light We were unable to secure a biopsy from the face of this patient for he refused this procedure However, the observations above are quite typical and leave little doubt that the origin of the colored secretion was from the apocrine sweat glands "abnormally" placed on the face

DISCUSSION

An examination of the literature concerning localized chromidrosis reveals striking similarities between our clinical cases and those described earlier (64-90) It is remarkable that so few cases were recorded after 1900 Actually, some 38 cases were described up to 1869, nine by LeRoy deMericourt alone, who gave the condition its name and later wrote a magnificent survey of the subject in 1884 The significant clinical findings and etiologic views for the great majority of the cases may be summarized as follows

1 Chromidrosis usually occurred symmetrically on the faces of young women (Fig 48) Most frequently, it had been seen on the lower eyelids but had usually been noted on other parts of the face also The abdomen chest, and thigh were involved occasionally The age range was from 15 to 57 years the average being 22 years The patients were in good health

2 In the vast majority of instances the color was black or very dark Brown, blue and yellow color tones were also described In more recent years (1934 1939) red sweat in the axilla following bismuth injections and in the perianal region have been reported also However aside from obvious cases of red chromidrosis due to external contamination with trichomycosis organisms in the axilla there were no other bona fide reports of red chromidrosis

3 The color appeared intermittently often 4 5 times a day and even during sleep It was preceded by a pricking or warm secretion Emotional stimuli such as fear anger, agitation and laughing regularly caused the secretion to appear Usually the problem was more severe in the summer In one instance the condition improved during lactation



Fig 48 Facial chromidrosis in patient described in [illegible] Illustration reproduced from lithograph in original article Patient noted onset of chromidrosis at age 15 Sweat was allowed to accumulate for 2 days on left half of forehead and for 5 days on right Lower eyelids also involved

4 A thick liquid secretion was seen initially This would dry rapidly to form an adherent glistening cap usually at the hair follicle Several observers described the dried secretion as having the appearance of dried varnish

5 Chemical studies revealed that the pigment was amorphous contained carbon and iron, was soluble in acids especially sul

furic and insoluble in water alcohol and ether Melanin, indigo, cyanurine, etc, could not be positively incriminated as the pigment involved

6 The source of the colored secretion was not agreed upon The sebaceous glands and eccrine glands were mentioned early as the sites of origin as was the pigmentary system of the eye Others believed it was due to bacteria or to external contamination with dirt, or carbon in the air

Colored skin secretions were described by Weber in 1888 in a study of the comparative physiology of mammals (93) He concluded that all such secretion arose from tubular glands The red sweat of hippopotami and kangaroos, the blue sweat of antelopes and the black sweat of gazelles were mentioned

Interestingly, Grieg also pointed out that milk and colostrum may at times be colored (98) Yellow, blue and green milk have been recorded by various observers

As stated, the origin of the colored secretion in our clinical cases with facial chromidrosis as well as our experimental subjects was the apocrine sweat glands of these areas All of the evidence, anatomic, physiologic and histologic, supports this conclusion as does comparative data on other mammals The vast majority of the cases described in the older literature are so remarkably similar to our own that we would postulate an apocrine gland source for the colored material observed in these cases, also

While we knew the glandular origin of this colored secretion, the precise abnormalities involved in apocrine gland function were still unknown It was not possible to study the colored material chemically because of the very minute quantities that could be secured

We directed our efforts to histologic and histochemical procedures to determine the nature of the pigment in the colored apocrine sweat The one constant change noted histologically in the chromidrotic apocrine glands both on the face (where the glands are small) and in the axilla was an increase in the number of pigment granules seen in the secretory cells (Fig 44) These granules are found in the gland producing white apocrine sweat in smaller numbers They are variably sized, round or oval at times irregular granules They may be found anywhere in the

cytoplasm but are most abundant supranuclearly In color they range from the large, round, golden-yellow variety to the smaller brown-black types Many of the cells may contain few or none of these granules Most possess a yellow autofluorescence and show the ability to reduce ferricyanide (Schmorl reaction) (Fig 46) Some of the granules show a positive test for iron Aqueous and hydrocarbon solvents do not remove these granules We found no qualitative difference between the granules of the chromidrotic and normal apocrine glands The difference was primarily quantitative The chemical nature of this pigment was the next question

Of the three main divisions of pigment, the *tyrosine* group (including melanin chromaffin and argentaffin granules), the *haem* group (porphyrin including hemoglobin and its derivatives) and the *lipopigments* (ceroid carotenoids and lipofuscin), we have eliminated the first two The members of the tyrosine group are nonfluorescent, and melanin stains were negative The porphyrin group was excluded on the basis of differential solubilities and fluorescence A comparison of the histo-chemical properties of the lipofuscin group with those of the pigment granules of the apocrine sweat gland convinced us that our pigment was a lipofuscin

The lipofuscins represent a broad spectrum of progressively oxidized compounds The lipid precursors at one extreme possess all of the chemical and physical characteristics of fats Gradually by a process of oxidation the following changes arise — the color increases and gradually darkens basophilia develops and increases in intensity and fat solubility and sudanophilia diminishes fluorescence is prominent in the intermediate stages but faces or is absent at the extremes Thus very light colored or very dark-colored lipofuscins do not fluoresce There is a progressive increase in the number of reducing groups reflecting their level of oxidation This is demonstrable by the Schmorl reaction which has been used as a test for lipofuscins

Ceroid is commonly viewed as a unique acid-fast pigment but is probably an intermediate form of lipofuscin Interestingly it was found in our chromidrotic glands but was absent in the normal ones lending support to the notion that lipofuscins are increased in amount in the chromidrotic gland

Iron does not appear to be increased in the chromidrotic apocrine glands It is possible however that it enters into the oxidation processes responsible for lipofuscin

We have not found significant effects on axillary chromidrosis following hormone administration or dietary restriction

Indican or indigo blue was excluded because of its inability to fluoresce and because it would not explain some of the other colors seen

Curiously, the apocrine glands of the ear canal in Caucasians and Negroes contain numerous lipofuscin pigment granules while those of the Mongolian show markedly reduced granule content It is to be recalled that the latter race also shows diminished apocrine sweat gland development in the axilla and elsewhere on the skin Paralleling this difference in granule content between these races is a difference in the color of the ear wax In Negroes and Caucasians it is yellow-brown while in the Mongolian it is usually colorless One might say therefore, that the former groups normally show chromidrosis of the ear canal

An attempt was made to examine colored apocrine sweat by means of ultra-micro-spectrophotometric techniques Dr Roy Korson of the Department of Pathology, University of Vermont School of Medicine, collaborated with us in this effort We sent Dr Korson samples of blue-black sweat from the faces of each of our clinical cases as well as two samples of greenish-blue apocrine sweat from the axillae of two of our experimental subjects for study Included also were five additional samples of white apocrine sweat for comparison Dr Korson s analysis of these specimens was consistent for all of the colored specimens studied and revealed the presence of two distinct pigments in the secretion each with characteristic absorption curves An alternative possibility was that one is an oxidation product of the other a notion much more likely according to our observations histochemically of the chromidrotic glands

In summary, localized chromidrosis is usually a disorder of the apocrine sweat gland regardless of its location on the skin surface The presence of apocrine sweat glands outside the usual apocrine areas is well-documented The pigment responsible for the coloration is apparently a lipofuscin which is found in the

pigment granules of all apocrine glands In the chromidrotic gland there is primarily an increase in the number of these granules although some increase in the state of oxidation may also be seen Thus, all apocrine sweat glands probably produce some pigment but because it is relatively small in amount or is diluted by larger amounts of colorless apocrine sweat, it is not seen In this regard it is noteworthy that white apocrine sweat dries to leave a yellow residue We interpret this as a concentration phenomenon Furthermore, although normal white apocrine sweat usually has a faint white fluorescence, many samples show a distinct yellow fluorescence This yellow fluorescence may be attributed to the presence of lipofuscin which may be detected more readily under Wood light than under visible light

Ordinary localized chromidrosis as seen in the axilla is a normal condition and as such, requires no treatment When the condition occurs on the face a cosmetic problem exists and some treatment is necessary

Topical measures are ineffective except to aid in the removal of the colored secretion Systemic measures such as anti-adrenergic drugs have not been satisfactory Destructive measures are impractical because of the large number of glands involved As stated dietary restriction of carotenoids is not helpful It is interesting to note in this regard that we were unable to induce axillary chromidrosis in twenty selected experimental subjects on a daily intake of 200 000 U of carotene for two months

C APOCRINE SWEAT RETENTION

1 Asymptomatic Apocrine Sweat Retention

In recent years great interest has been evinced in the effects of *poral closure* on the various appendages of the skin The pathogenesis of the various forms of miliaria is clearly a result of ductal obstruction (99 100) Extension of this concept to include *diseases of the sebaceous glands*, the acneiform dermatoses has also been recognized and occlusion of the sebaceous duct with keratin is considered a fundamental step in the development of these disorders (101 102)

Little effort has been made to examine the effect of ductal obstruction on the diseases of the apocrine sweat gland Because

we felt that this process may be of prime importance in the apocrine disorders, we proceeded with the following studies (103)

Method and Materials

Seven healthy adult White males between the ages of 20 and 28 were selected for this study Antiperspirants had been interdicted for at least one month

The axillae of these subjects were shaved and the apocrine sweat glands emptied by the local subcutaneous injection of 0 15 cc 1 1000 epinephrine solution When the apocrine sweating had subsided 5-10 axillary hairs in a circular area (½ inches in diameter) were plucked with a fine forceps These follicular orifices were then treated in either of the following ways

(a) Application of concentrated nitric acid, or

(b) Electrodesiccation (Bovie Unipolar setting at 5)

In addition several extra-follicular apocrine duct orifices were similarly damaged

Three days later, the apocrine sweat glands were again stimulated in these subjects by the local injection of 0 15 cc 1 1000 epinephrine Biopsies of the treated axillae of two of the seven subjects were then taken after local procain anesthesia in a "block' technique The other subjects were again examined for apocrine anidrosis (epinephrine stimulation locally) and then biopsied at 7 (two subjects) 9 14 and 21 days Tissues were fixed in formalin, sectioned serially and stained with hematoxylin and eosin

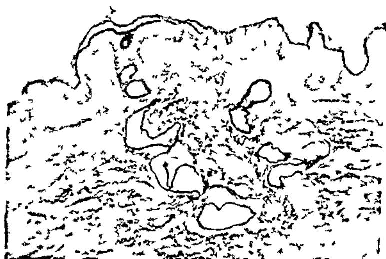
Observations and Discussion

In all of the subjects examined, apocrine anidrosis resulted This anidrosis was evident as early as 3 days after treatment and persisted throughout the three week observation period Under stereoscopic microscopy (30x) one could usually outline a small keratin plug' in these follicular orifices This was especially prominent at the 7-9 day period

Miliarial changes were absent at these sites and *no clinical* signs either objective or subjective, were discernible except for slight erythema during the first 2-3 days following the application of the acid or electrodesiccation

The pathologic alterations of the apocrine sweat gland which occurred secondary to these damaging procedures were at a





F g 49 Kerat n plug n apoc ne d ct B opsy of axill ı skin 7 d ıys after aj] l cat on of concentrated nitr c a d sl o s c mj act kerat no s plug of apocr n duc *Contrast th s keratın w h the normal loose f brillar mater al ın tl e l a r foll cle* H a d E Mag x 300

F g 50 D late l apo rine du l e ult ng f om poral o lus on (7 d ıy) Sect n of ax llary sk n shov ıng extra foll cular apocr ne duct with occlusive kerat n j lug and progress ve dilatat on of the duct do vnward Duct vas traced t aj ocr ne gland belo v H and F Mag x 160



Fig 51 Apocrine sweat retention — 14 days Low power view of histology of apocrine sweat retention process Observe compact keratinous plug in apocrine duct orifice plus dilated segmen of duct below Some portions appear to be almost cystic H and E Mag x 35

histologic level They are illustrated in the photomicrographs (Figs 49-55) and are listed below, viz

(1) Focal hyperkeratosis and keratin plugging of the hair follicles and apocrine ducts both follicular and extra-follicular

(2) Dilatation of the apocrine duct progressively down toward the apocrine tubule In some instances there was near cystic change of the duct (Fig 54) and dilatation of the tubules Extreme



Γg 5? D lated afo n du t ?I day Ano her extra foll cular ap rin d ct sho ving the sequence of changes in s eat retent on keratin ,l g in duct le or fce and d lata on of d s al segm nt of tl e du t H and Γ Mag x 16)

flattening of the lining cells was seen alon, with lumin il casts in many sections These changes were *not* evident in the biopsies removed 3 days after follicular damage At this stage the glands appeared normal except for tl e keratin plugs above The m ximal dilatation and cellul ir flattenin w is seen in the 7) d iy pec mens At 14 and 21 days these ch inges did not appear to le increased nor was definite evidence of glandul ir rupture present



Fig. 53. Dilated apocrine duct with cast, 7 days. Nearly transverse section of dilated apocrine duct just beneath poral block. Trapped apocrine sweat is evident as cast in lumen. H and E. Mag. ×250.

Fig. 54. Cystic apocrine tubules. Section showing markedly dilated cystic apocrine tubules visualized 21 days after poral occlusion. Cast in cystic tubules is apparent. Contrast cell height of adjacent normal apocrine tubules with that of the cystic ones. H and E. Mag. ×90.

(3) These sections were otherwise normal in every respect Furthermore, the sebaceous glands appeared unaltered

Comment should be made regarding the techniques *employed* to close the follicular orifices While it is relatively easy to produce eccrine duct occlusion with the milder injury produced by maceration ultraviolet light or adhesive tape, it is apparent that greater *injury is necessary to close the more patulous hair follicle orifice* Concentrated nitric acid and electrodesiccation were utilized effectively in this respect Both techniques allowed for the treatment of a single hair follicle orifice The acid was of additional value since it flowed down into the hair follicle and produced damage along its path including the rather superficially placed apocrine duct orifice The presence of a terminal hair was something of a detriment to our *plugging* technique *and prompted* an additional preliminary step in this procedure, viz, removal of the hair with forceps Apparently the hair acted as a stylette in maintaining patency

The subjects were not examined before 72 hours since studies on the physiology of the apocrine sweat gland showed that apocrine sweating cannot be induced for 24 48 hours after complete emptying of the gland This refractory period is necessary for refilling of the tubular reservoir with apocine sweat

The progressive dilatation of the apocrine duct and tubules confirms the purely mechanical nature of these changes The gradual secretion of apocrine sweat in this closed system is accompanied by an increase in intraluminal pressure with consequent ductal and later tubular dilatation Eventually this pressure arrests further secretion Apparently the duct is the more distensible *part of the apocrine glandular system* perhaps because of an absence of myoepithelium

Examination of routine axillary biopsies has indicated that asymptomatic apocrine sweat retention occurs rather commonly for it is not *unusual* to see *changes in the so-called normal*' axillary skin which closely resemble those experimentally produced here

The extreme flattening of the apocrine cells seen in these sections was thought heretofore to represent either a resting gland or atrophy of the tubular cells of undisclosed origin As



Fig 33 Fibrosis about dilated apocrine tubule 14 days Dilated apocrine tubule showing peri tubular fibrosis This was a late but not constant finding as a consequence of apocrine sweat retention H and E Mag × 300

is clearly demonstrated in this study, the low cuboidal state of the apocrine gland cells in the resting or early secretory phase can be easily distinguished from the markedly flattened atrophic cells of the "blocked gland These atrophic tubules are more common in the axillary skin of the aged patients The absence of an inflammatory reaction accompanying these changes is not surprising

Rupture of the apocrine system did not occur even at 21 days It is to be recalled that such a 'break" is necessary in the production of miliaria, with resultant eccrine sweating *into* the skin Such factors as infection endocrine variation and individual susceptibility may so modify the apocrine sweat gland so as to permit such a rupture At any rate at the end of this study it was our feeling that rupture of the apocrine system was requisite for the production of the clinical changes as seen in Fox Fordyce disease and hidradenitis suppurativa

2 Fox-Fordyce Disease

This disorder is characterized by the presence of numerous pruritic papules primarily follicular in location in apocrine gland

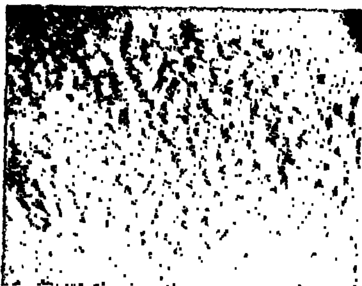


Fig 56 Clinical appearance of Fox-Fordyce disease in axilla Photograph of axillary skin of 19 year old girl showing follicular papules characteristic of Fox Fordyce disease

bearing areas such as the axillae, pubes mammary areola and so on It occurs predominantly in females and often appears during early adolescense or just after puberty Pruritus is frequently related to emotional stimulation although often occurs spontaneously Generally the course of the disease is progressive involving more and more of the apocrine areas, although unexplained remissions have been described Peculiarly the disease frequently abates completely during pregnancy, even with clearing of the skin lesions, only to recur during the puerperium Treatment has been uniformly unsuccessful over the years

Examination of the involved skin of patients with Fox Fordyce disease will reveal some loss of axillary hair in many cases but except for the *follicular papules, these areas show no abnormalities* (Fig 56) Our early studies of patients with this disease revealed apocrine anidrosis in the region of the papular lesions In three cases studied after local epinephrine or pitocin, no apocrine sweat could be made to appear in the involved areas The patients usually experienced some pruritus in these areas after such stimu-

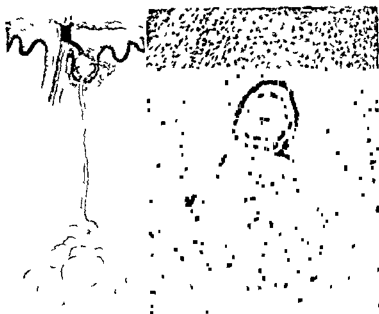


Fig 57 Diagram showing development of Fox Fordyce disease Schematic drawing showing point of rupture of apocrine duct in Fox Fordyce disease

Fig 58 Pathology of Fox Fordyce disease Pathognomonic vesicle of Fox Fordyce disease found at a level of the intra epidermal portion of the apocrine duct Compare with Figure 57 H and E Mag x 400

lation These observations led us to believe that apocrine sweat retention was a feature of these lesions

In the previous section we described subclinical changes which can occur in the apocrine sweat gland as a result of experimentally produced poral closure These changes were revealed after careful study of serial sections of the involved skin Shelley and Levy have described a second change resulting from occlusion of the apocrine sweat duct (104) This consisted of a rupture of the epidermal duct as a result of the increasing distention and the formation of a sweat retention vesicle within the epidermis (Fig 57) Actually, this vesicle is formed in the intra epidermal portion of the apocrine duct (Fig 58) It appears that in addition to the spongiosis and edema produced there is also acanthosis of the epidermal cells surrounding this portion of the apocrine duct In this regard, it is significant that Hambrick and Blank have

described thickening of the apocrine duct in whole mounts of the axillary skin of patients with Fox-Fordyce disease (105) Their studies were at a comparatively gross level however, and did not reveal the changes evident microscopically as described above It should be emphasized that visualization of the sweat retention vesicles of Fox-Fordyce disease may be impossible unless one does serial sections of the tissue Moreover, individual susceptibility allowing ductal rupture to occur is essential for the production of this disease In the absence of this rupture, which is apparently due to an inherent weakness of this tissue, there would be only anidrosis and possibly dilatation of the duct with eventual shut-down of the apocrine secretion In miliaria, a similar story with regard to eccrine duct rupture has been told Finally, the pruritus of eccrine miliaria and Fox-Fordyce disease is caused by extravasation of apocrine sweat into the epidermis

There is no adequate treatment for this disease At present, our only approach is symptomatic, directed toward relief of the pruritus

Antipruritic lotions corticosteroid lotions and sprays and sedation have been used with some success Temaril ®, in doses up to 20 mg a day has been helpful in some cases but often fails to relieve the intense paroxysmal pruritus associated with this condition X-ray is of no value in the management of this disease and systemic corticosteroids are not recommended since their prolonged use in moderate to high dosage is required for relief of symptoms Antibiotics systemically and local, should be employed in those cases in which secondary infection is present In recent years marked improvement in several patients with this disease has been achieved with estrogens in dosages higher than those previously used Premarin® up to 5 mg daily seemed to accomplish an involution of the process (110) Further clinical study with this drug is necessary to confirm its efficacy in this disease, however

3. Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic cicatrizing suppurative process involving the apocrine gland-bearing regions primarily the axillae and ano-genital areas It usually begins as a small, firm erythematous lesion fairly deep-seated and painful Occasionally these subside clinically More often however the



Fig 59 Clinical view of hidradenitis suppurativa Photograph shows dense scarring and sinus tracts typical of hidradenitis suppurativa Process involves most of axilla Inguinal involvement was also observed in this patient

process extends beneath the skin producing larger confluent masses These eventually erode through the skin producing sinus tracts and healing with thick scars (Fig 59) The ultimate outcome is a more or less chronic suppurative process, with draining sinus tracts and cicatrization Exacerbations, which consist essentially of acute abscesses, occur at irregular intervals At times hidradenitis and Fox-Fordyce disease may coexist (112)

In five cases studied clinically by us, we were impressed by the fact that as in Fox-Fordyce disease the areas of involvement with hidradenitis show apocrine anidrosis This would obviously be found in a far advanced case with much scarring and fibrosis However, we examined early lesions where scarring was absent and the absence of apocrine sweating (after local pharmacologic stimulation with epinephrine), was quite evident This lead us to believe that this disease was also the result of apocrine sweat retention, with rupture of the apocrine system but with the added factor of bacterial infection

An extension of our original experimental studies on the effects of apocrine sweat retention by Shelley and Cahn proved this concept to be correct (106) These authors produced keratinous plugging in the axillae of 12 normal adult male subjects by the application of perforated belladonna adhesive tape to a skin area that had been manually epilated All of the subjects developed apocrine anidrosis in these areas at the end of one week In three of the twelve, however, *clinical evidence of hidradenitis was* observed Three men presented small, deep tender nodules sharply localized to the tape sites Histological study of these early cases revealed the following changes (1) keratinous plugging of the apocrine duct, (2) dilatation of the apocrine duct, (3) severe inflammatory changes limited to a single apocrine sweat gland The dilated apocrine duct became filled with polymorphonuclear leucocytes The bacteria, which had been trapped beneath the keratinous plug multiply rapidly, finding apocrine sweat an excellent milieu Subsequently, rupture of the apocrine duct occurred with spread of the pyogenic process through the dermis Because of the proximity of the apocrine sweat glands to one another as illustrated in an earlier section, it is easy to understand the ready extension of the process to other glands

It should be stressed that eventually, many or most of the apocrine sweat glands are destroyed by this same inflammatory reaction, leaving fibrous and isolated atrophic tubular remnants This is what is visualized by the pathologist as he studies a biopsy of advanced or chronic hidradenitis suppurativa *It is only by* reproducing the disease experimentally and examining carefully the early changes histologically, that an accurate reconstruction of the pathogenesis of this disease can be made

Treatment of hidradenitis is usually quite satisfactory if the process is seen early Antibiotics, in adequate dosage and local anti-bacterial measures are effective at this time

Tight fitting apparel is to be strictly avoided In resistant cases, management may be extremely difficult X-radiation has been advocated but we are not impressed with its effectiveness Exposure and destruction of residual, chronically infected sinus tracts may be beneficial in those chronic cases in which the process has become localized to such foci Some have used the electro-

coagulating current to destroy such exposed foci As more and more glands are destroyed or fibrosed secondary to the inflammatory process, the disease may tend to "burn itself out" In severe protracted forms of the disease extensive surgery with excision of the involved area and full-thickness skin grafting may be necessary Even with this more radical approach, however, recurrences may be seen Corticosteroids have recently been used with success in the treatment of this disease Hydrocortisone, in doses up to 80 mg per day or other steroids in comparable dosage when maintained at this level for 1-2 weeks and then grdaually reduced and stopped within 4-6 weeks has been quite helpful in a number of cases (111) The mechanism of action is unknown but may be a local anti inflammatory effect and–or result from a depression of pituitary activity, with some possible diminished apocrine secretion

VI

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